Audit of failure rate of Coartem™ to treat falciparum malaria at single fourteen-day follow-up

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Summary

Objective.
To assess the failure rate of the new first line treatment regime for uncomplicated falciparum malaria in KwaZulu-Natal of Coartem™ tablets (20mg artemether and 120mg lumefantrine – Novartis South Africa (PTY) Ltd).

Design.
A before-after study[1].

Setting.
Ndumo Clinic, Ingwavuma District, KwaZulu-Natal, South Africa, February 2001.

Study Group.
67 patients presenting to Ndumo clinic with uncomplicated malaria. diagnosed by symptoms and positive immunochromographic test for plasmodium falciparum.

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

Results.
All of the 58 follow-up slides obtained were negative. 8 patients failed to return, and 1 slide washed off. Only 43 smears were positive at day 0 of which 36 had follow-up smears.

Conclusions.
No resistance to Coartem™ was shown at day 14, and Coartem™ has been shown to be more effective at clearing falciparum malaria parasites than a previous regime of sulfadoxine/pyrimethamine with chloroquine.

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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 cases detected through active and passive surveillance.

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 serving an area with the highest incidence of malaria in South Africa, cases detected increased from 637 in 1995, to 2 972 in 1998, 17 420 in 1999, and 30 822 in 2000, requiring the aid of the South African Defence Force. In 1995 there were 5 992 notified cases of malaria in South Africa[3], whereas from January to May 2000 there were 36 717 notified malaria cases[4].

From January to April 2000 an in vivo study[5] 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 for the remainder of 2000.

An audit[6], by the authors, of the efficacy of CQ combined with SP at single 14 day follow up at Ndumo Clinic in October 2000, showed failure to clear parasites in 15/55(27%) patients asked to return and 15/37(41%) of those who actually returned.

In January 2001 SP ceased to be issued by the Department of Health Pharmaceutical and Medical Supplies Centre for treatment of malaria in KwaZulu-Natal. Coartem™ (tablets containing 20mg artemether and 120mg lumefantrine – Novartis South Africa (PTY) Ltd) became the recommended treatment for uncomplicated malaria in non-pregnant patients aged more than 1 year[7].

Having demonstrated unsatisfactory results with an audit6 * MERGEFORMAT of SP combined with CQ, and the recommended treatment for uncomplicated falciparum malaria then having changed to Coartem™, it was desirable to complete the audit cycle with an assessment of the new regime.

A standard WHO protocol for assessment of therapeutic efficacy of antimalarial drugs[8] requires follow-up of patients on at least days 0,1,2,3,7 and 14. Substantial resources are needed, and preventing patients dropping out is difficult.

Current 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.

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]. Considering that the treatment course for Coartem™ is 3 days, it is unlikely that parasites would appear due to reinfection rather than resistance before 14 days. After 14 days techniques such as polymerase chain reaction are needed to distinguish between malaria recrudescence 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).

With the previous audit of SP and CQ[6], the guidelines were applied in the form of a single 14-day follow-up of a sample of patients, as a quick and simple assessment of the efficacy of the regime. For the same reasons, and to help comparison with the audit of the previous regime, the same 14 day

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.

interval was chosen for the audit of Coartem™. A wider age range was accepted for this Coartem™ audit compared to the 16 years or over used for audit5 of SP and CQ to ease recruitment in the face of a decrease in malaria incidence during December 2000 and January 2001, probably due to enhanced control measures.

Study Population and Methods

Sample size was calculated according to statistical considerations in a World Health Organisation protocol[8] MERGEFORMAT, 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, using small sample sizes. Taking a 25% failure rate to be certainly unacceptable, but less than 10% to be 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 low failure rate (type 1 error), whilst being 80% sure of not erroneously concluding there to be a high failure rate when it is really less than 10% (type 2 error). Using this method and applying the given thresholds, either no failures from a sample of 16, or between 1 and 5 treatment failures from a sample of 42 could be considered acceptable, but more than 5 treatment failures would be unacceptable, and not significantly less than 25%. To allow for dropouts, 67 patients were invited to return for follow-up.

Figure 1: Age distribution of sample asked to return for fourteen-day follow-up after treatment with Coartem™. Ndumo Clinic, Feb 2001

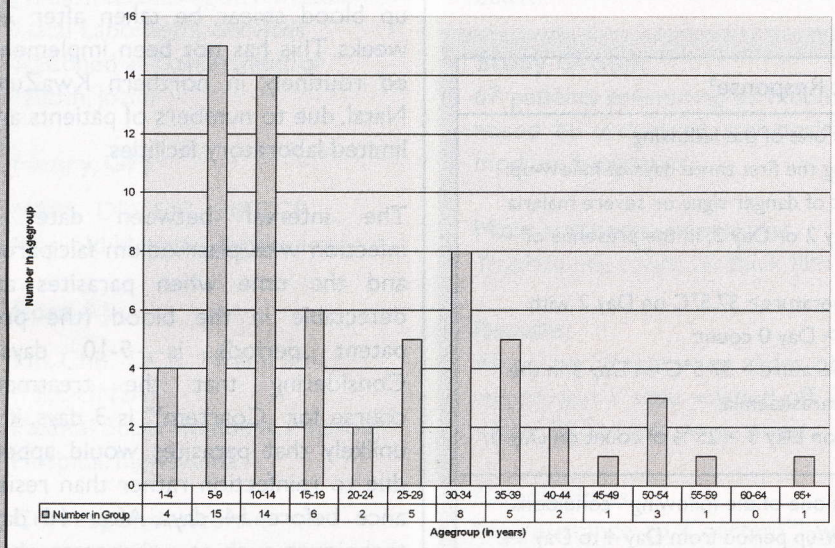

Table II: Malaria Treatment Guidelines (uncomplicated falciparum malaria) KwaZulu-Natal – 20017

Weight	Number of Coartem™ tablets per dose (given twice daily over three days)
10-<15 kg	1
15 - <25kg	2
25 - <35kg	3
35 + kg	4
65 + kg*	4

*Patients weighing more than 65kg have not been well studied.

In February 2001, over six working days, 67 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, or in the case of children, the accompanying adult 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 less than 1 year and patients treated for malaria during the previous two weeks were excluded from the audit. The age distribution of subjects asked to return is given in Figure 1.

Thick blood films were taken. Patients were given the recommended treatment for uncomplicated malaria in KwaZulu-Natal[7] MERGEFORMAT, which is given in Table II.

Patients were given a piece of paper with the follow-up date, and were offered R30 for travelling expenses and a mosquito net on return. Patients were told to return immediately should their condition deteriorate. Upon their return, patients were clinically assessed, temperature taken, asked whether they thought they had suffered any side effects from Coartem™, and thick blood film made.

Thick blood films were allowed to dry for 24 hours, then stained with 10% Giemsa (5ml Giemsa diluted with 45ml phosphate buffer) for 10 minutes, rinsed with tap water and air dried. They were then examined using 100x oil objective. Malaria parasites were counted in conjunction with 300 white cells. The number of parasites so counted was multiplied by 25 to give an estimate of the number of parasites per microlitre of blood.

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

Results

The results may be summarised as in Table III:

Patients were compliant with follow-up, only 8 out of 67 failing to return, despite wet weather for much of the follow-up period. 6 dropouts had been day 0 thick film positive.

24/67 patients could not be demonstrated to have parasites on thick film on day 0, despite being positive on immunochromograhic test (ICT) for falciparum malaria.

One slide at day 14 washed off, the patient having been thick film positive at day 0, hence only 36 of the day 0 film-positive patients had follow-up films.

One patient returned at 7 and 14 days and was thick film negative on day 0,7 and 14. One patient returned at day 13 instead of 14. One patient had high parasitaemia of 9675 parasites/µl but was thick film negative at day 14. All other parasite counts were less than 1000/µl at day 0. There were 8/67 patients weighing more than 65kg. Only 4/8 of these patients were day 0 film positive. All 8 returned for follow-up and were day 14 film negative.

No gametocytes or other species than falciparum were seen either before or after treatment. As in an earlier audit of SP combined with CQ5, parasites were often atypical, seen as chromatin dots rather than ring-forms.

Symptoms were mild:

At day 0:
9/67 patients had fever 37.1 – 37.9°C
6/67 patients had fever of 38°C or more

At follow-up (day 14 for all but 1 patient who was day 13):
10/59 patients had fever 37.1 – 37.9C; 2/59 patients had fever of 38C or more.

No symtoms suggesting side effects were reported. 56/58 patients felt improved. Of the two not improved, one complained of sore throat and headache and the other of sweats and palpitations.

9/58 patients reported symptoms at follow-up. These were, with frequencies of reporting: cough[3]; headache[3]; blood in urine[2]; fever, sore throat, palpitations, sweats, shivering and decreased appetite[1].

It is worth noting that bilharzia is very common in the Ndumo area. Of interest is that 7 patients inadvertently had repeat ICT test on day 14, and 6/7 of these tests were still positive.

Table II: Results of follow-up of patients after receiving Coartem™, Ndumo Clinic, February 2001

Patients asked to return for follow-up	67
Patients returning for follow-up	59
Patients who had parasites seen on thick film at day 0	43
Patients returning who had parasites seen at day 0	37
Patients with parasites at day 0 and follow-up film result	36
Follow-up thick films positive (with or without parasites seen on day 0)	0

Conclusions

An unexpectedly high number of patients (24/67) were thick smear negative at day 0. During a previous audit[6] MERGEFORMAT only 2/76 patients who were ICT positive failed to show parasites on thick film. A contributing factor may have been that the medical officers took too thin a blood film, as was commented soon afterwards by the medical technologist. Thicker films were taken at follow-up.

36/36 patients were demonstrated to clear parasites by day 14 with Coartem™. The fact that there were no failures from a sample of 36 means that using the Double Lot Quality Assurance method[8] MERGEFORMAT it can be concluded confidently that there are less than 25% failures. In fact the sample size is large enough to be confident that the day 14 failure rate is less than 15% ($P<0.05$).

It is also of note than none of the 58 follow-up slides on patients who

were ICT positive at day 0 showed parasites, as it is likely that most were parasitaemic, even if counts were too low to visualise in a thick film in 22 of those cases. No resistance to Coartem™ was shown at 14 days. Coartem™ has been shown to be more effective than the previous regime of sulfadoxine/pyrimethamine combined with chloroquine, for which a day-14 failure rate of between 27 and 41% was demonstrated MERGEFORMAT [6].

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