



**Therapeutic efficacy of chloroquine and
sulphadoxine-pyrimethamine in the
treatment of uncomplicated falciparum
malaria, Khanabad, north-eastern
Afghanistan, October 2002-February
2003**

Preliminary report

**MERLIN (Medical Emergency Relief International)
and the
Institute of Malaria and Parasitic Diseases**

Supported by WHO Afghanistan



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Background and rationale

Malaria is endemic with seasonal transmission in Afghanistan, particularly at altitudes below 1500m and near rice growing areas of the east and north east of the country. Recorded incidence in these areas is the highest in the country, more than 500/10,000 population in 2002¹ (and the true incidence is estimated to be at least 6 times the recorded incidence). Incidence exhibits a bimodal pattern, with vivax incidence peaking in July and August and falciparum malaria in October.

Malaria incidence has been increasing steadily since the winding down of the malaria eradication programme commencing in 1979. Falciparum malaria, once nearly eradicated, accounted for some 20% of reported confirmed malaria cases in 2002². The spread of chloroquine resistance, the most widely used antimalarial drug, is likely to be a contributing factor to the increase in falciparum malaria.

Chloroquine has been widely used in the treatment of uncomplicated malaria in Afghanistan since the 1940's, and remains first line therapy in the national protocol, with sulphadoxine-pyramethamine as second-line therapy. Chloroquine resistance was first reported in Afghanistan in 1986³. In 1999, 67% treatment failure was reported from a study conducted on children greater than 7 years of age in eastern Afghanistan (11% after 7 days of treatment, 55% after 14-28 days)⁴.

One of the cornerstones of malaria control is access to effective antimalarial treatment⁵. To guide the development of national malaria treatment policy for Afghanistan, antimalarial drug efficacy data is required. A WHO TDR-funded study is underway in Jalalabad, eastern Afghanistan, conducted by HNI. Data from north-eastern Afghanistan is also required.

¹ Institute of Malaria and Parasitic diseases, unpublished data

² Institute of Malaria and Parasitic diseases, unpublished data

³ Delphini LF (1989) The first case of *Plasmodium falciparum* resistance to chloroquine treatment discovered in the Republic of Afghanistan. *Transaction of the Royal Society of Tropical Medicine and Hygiene*, 83, 316

⁴ Rab MA, Freeman TW, Durrani N, De Poerck D, Rowland M. (2001) Resistance of *plasmodium falciparum* malaria to chloroquine is widespread in eastern Afghanistan. *Annals of Tropical Medicine and Parasitology* 95, 41-46

⁵ World Health Organization; 2000. African summit on Roll Back Malaria, Abuja, Nigeria, April 25 2000 WHO, Geneva, Switzerland WHO/CDS/RBM/2000.17.

Patients and methods

The study was conducted in a Swedish Committee of Afghanistan (SCA) supported primary care clinic located next to a dilapidated but functioning MOH supported malaria clinic remaining from the former malaria control programme. Patients were recruited from patients attending both clinics for febrile illness. The clinics are located in Khanabad, a district capital in the province of Kunduz in north-eastern Afghanistan, close to the border with Tajikistan. The study was conducted by the MOH and the international NGO MERLIN with support from WHO and the collaboration of SCA.

A 28 day *in vivo* efficacy study of chloroquine and sulphadoxine-pyramethamine (SP) was conducted using modified WHO protocol⁶⁷. The study was commenced on 20 October 2002 during the period of peak falciparum malaria incidence. Inclusion criteria were: history of fever in the past 24 hours; over 6 months of age; Giemsa-stained slide positive *Plasmodium falciparum* mono-infection with parasite density of 1000-100000 parasites/ μ l; live within one-hour's car journey of hospital; and informed consent. Exclusion criteria were: any sign of severe disease; pregnancy; currently in treatment for malaria; and febrile disease other than malaria. Pre-treatment with chloroquine or other antimalarial drugs on self-report was not considered and exclusion criterion.

All patients were reviewed clinically and parasitologically. Those meeting all inclusion criteria and having no exclusion criteria were enrolled in the study. Patients were recruited sequentially initially into the chloroquine treatment arm (October 20 to December 8) and then into the SP arm (15 December 2002 to February 5 2003).

Patients were weighed and given supervised dosing of 25mg/kg over three days (10mg/kg days 0 and 1, 5mg/kg day 2) of quality-controlled chloroquine (IDA) or single dose 25mg sulphadoxine component/kg of quality-controlled SP (CREAT SA France). Patients were observed for 30 minutes following each dose.

Parasitological follow-up occurred on day 2, and parasitological and clinical follow-up occurred on days 3, 7, 14, 21, 28 and any other day the patient complained of symptoms. Slides were cross-checked externally by reliable microscopists.

Outcomes were classified as

Early treatment failure (ETF), if on days 1-3 the patient suffered from severe illness or severe malaria; or if on day 2 parasitaemia was greater than on enrollment; or if parastaemia on day 3 was more than 25% than parasitaemia on

⁶ World Health Organization; 1996. Assessment Of The Therapeutic Efficacy Of Antimalarial Drugs For Uncomplicated Falciparum Malaria for Areas of Intense Transmission. WHO, Geneva, Switzerland. WHO/MAL/96.1077

⁷ *Monitoring Antimalarial Drug Resistance*, Report of a WHO consultation. WHO, Geneva, Switzerland 3-5 December 2001 WHO/CDS/CSR/EPH/2002.17 WHO/CDS/RBM/2002.39

enrollment; or if there was persistent fever in the presence of parasitaemia on day 3.

Late clinical failure (LCF), if the patient suffered from axillary temperature $\geq 37.5^{\circ}\text{C}$ or gave a history of fever in the previous 24 hours in the presence of parasitaemia on days 4-28.

Late parasitological failure (LPF), if parasitaemia was recorded on days 7 – 28 without symptoms.

Results and discussion

Chloroquine study

Summary results from cross-checked data for 57 enrolled patients are given in Table 1. Early treatment failure accounted for 5.3% of cases (3/57, 95CI 1.4-15.5%), late parasitological failure for 84.2% (48/57, 95CI 71.6-92.1%) and only 10.5% (6/57, 95CI 4.4-22.2%) classified as adequate clinical and parasitological response. No patients in the corrected sample were classified as late clinical failure. The overall treatment failure rate was recorded as 89.5% (51/57, 95CI 77.8-95.6).

Table 1. Summary results from chloroquine efficacy study

| | |
|---|-------------------|
| Drug | Chloroquine (IDA) |
| Location | Khanabad |
| Dates | 20/10-8/12/2002 |
| Number of patients included in analysis | 57 |
| Female | 37% |
| Under five years of age | 11% |
| 5 to 15 years of age | 61% |
| Older than 15 years of age | 28% |
| Dose mean (range) mg/kg | 27 (25-43) |
| Parasitemia geometric mean (range) / μl on enrolment | 5868 (1000-80000) |
| Duration of follow up | 28 days |
| ACPR | 6 (11%) |
| ETF | 3 (5%) |
| LPF | 48 (84%) |
| TREATMENT FAILURE RATE | 90% |

Sulphadoxine-pyrimethamine (SP) study

Summary results are shown in Table 2 for 66 enrolled patients. Only one patient reported having taken chloroquine prior to entering the study, and this patient subsequently went on to be classified as late treatment failure. Results revealed one late clinical failure (1.5%, 95CI 0.1-9.3), and 15 late parasitological failures (21.2%, 95CI 12.5-33.3), with an overall treatment failure rate of less than one quarter (22.7%, 95CI 13.7-35.0). The majority (51/66, 77.3%, 95CI 65.0-86.3) were classified as adequate clinical and parasitological response. Of those failing treatment, 9 failed day 7, and 2 failed on each of days 14, 21 and 28.

Table 2. Summary results from SP efficacy study

| Drug | SP (Creat SA) |
|---|---------------------|
| Location | Khanabad |
| Dates | 15/12/2002-5/2/2003 |
| Sample size | 66 |
| Dose mean (range) mg/kg | 26 (22-43) |
| Duration of follow up | 28 days |
| Parasitemia geometric mean (range) / μ l on enrollment | 5470 (1076-36800) |
| Parasite clearance by day 3 | 50 (66%0) |
| Cumulative incidence treatment failure (parasitological evidence) | |
| Day 7 | 14% (+9) |
| Day 14 | 17% (+2) |
| Day 21 | 20% (+2) |
| Day 28 | 23% (+2) |
| Classification of outcome | |
| ACPR | 51 (77%) |
| LCF | 1 (2%) |
| LPF | 14 (21%) |
| TREATMENT FAILURE RATE | 23% |

The SP study was completed during the winter non-transmission season, which may bias the study towards selection of recrudescing cases that may be more likely to be resistant to chloroquine, the most widely used antimalarial drug, and perhaps other antimalarial drugs. The results shown may be an overestimation of true failure rates for SP. Thus SP remains efficacious with less than 25% treatment failure.

Conclusions and recommendations

The results suggest that CQ is no longer efficacious for the treatment of uncomplicated falciparum malaria, with approximately 90% treatment failure observed. Chloroquine should no longer be used as a first-line drug for the treatment of uncomplicated falciparum malaria.

SP remains efficacious, with less than 25% treatment failure observed. SP, particularly in combination with an artemisinin derivative, would be an appropriate choice for first line therapy of uncomplicated falciparum malaria. This combination has the advantage of being clinically efficacious as well as potentially delaying the development of resistance to SP (as has been shown to occur rapidly in other settings of low to moderate transmission where SP is used as monotherapy). In addition, the combination SP plus artesunate may decrease transmission because of the gametocidal effect of artesunate⁸.

This combination would not be appropriate for the treatment of vivax malaria, in view of the poor action that SP usually has against this species. Chloroquine

⁸ Antimalarial drug combination therapy: report of a WHO technical consultation. WHO Geneva 2001; The use of antimalarial drugs: report of an informal consultation WHO Geneva 2001 WHO/CDS/RBM/2001.33

remains the drug of choice for treatment of vivax malaria in Afghanistan. Therefore efforts must be made to improve access to quality diagnostic services.

Efforts should be made to develop standardized national malaria treatment protocols in light of these and other data. Sentinel sites should be established in at least two epidemiological settings of adequate technical capacity to monitor the therapeutic efficacy of antimalarial drugs in Afghanistan to accompany the introduction of new treatment regimes.