

A RANDOMISED CLINICAL TRIAL COMPARING THE EFFICACY OF B- ARTEMETHER AND CHLOROQUINE FOR THE TREATMENT OF UNCOMPLICATED MALARIA IN TANZANIA

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ABSTRACT: A randomised clinical trial was conducted in the Muheza Designated District Hospital (Teule) to compare artemether with chloroquine for tolerance and efficacy in treating malaria. Patients aged 5 years and above were screened clinically and parasitologically. Chloroquine was administered at 25 mg/kg of body weight over 3 days. Artemether was given at 3.2 mg/kg on the first day, and 1.6 mg/kg on the following four successive days. 54 patients were treated with chloroquine and 52 with artemether. The latter drug demonstrated a rapid, progressive and significant effect from day 3. It scored its highest parasite clearance of 92.2% on day 7, in contrast to 57.7% achieved by chloroquine on the same day. No difference in the clinical response observed between the two drugs. Adverse effects were mild and negligible, and consisted of itching and dizziness. No abnormal physiological function tests noted. Thus, oral artemether was highly effective in clearing parasitaemia compared to chloroquine, and virtually had no side effects.

Introduction

Malaria is an increasing public health problem worldwide. It is endemic in over 90 countries, poses an infection exposure risk to over 40% of the world's population,

and each year about 300 million people become infected, resulting to over 2.7 million deaths (WHO, 1996). The problem is compounded by the emergence, and rapid spreading of multi-drug resistant strains of *Plasmodium*

falciparum. In the united Republic of Tanzania malaria is mostly caused by *P. falciparum*, and accounts for over 30% of the disease burden (World Bank). Furthermore, there are already high levels of parasite resistance not only to the first line drug, chloroquine (CQ), but also to the second line and reserve drugs. The *in vivo* and *in vitro* studies undertaken in Tanga region in the north-eastern part of the country elicited parasite resistance rates of 40%, 70 – 75% and 5% to CQ, sulfadoxine/pyrimethamine (SP) and mefloquine (MQ), respectively (Kilimali and Mkufya, 19885a; Kilimali and Mkufya, 1985b; Kilimali *et al.*, 1989; Ronn *et al.*, 1996). Nevertheless, prompt and effective case management remains the most important control method, which therefore, justifies concerted research efforts to provide alternative antimalarial drugs.

The Chinese herb, *Artemisia annua*, also known as qinghao in China was used for the treatment of malaria in the People's Republic of China for time immemorial. The active component of the herb, artemisinin (known in Chinese as qinghaosu) was isolated and characterised by Chinese scientists in 1972, and the compound and several of its derivatives have been studied for efficacy, pharmacology, pharmacokinetics and toxicology (WHO, 1993). Artemether (AT) is one of the derivatives of artemisinin that has shown to have great antimalarial activity. Its initial clinical trials, most of which were conducted in the Far East and several African countries other than Tanzania, showed that the drug was safe, well-tolerated and effective in clearing parasitaemia and malaria related manifestations. The side effects observed with this drug were mostly associated with the injectable (intramuscular) preparations, and in all cases they have been of low incidence, mild and transient. In view of the occurrence of rapid spread of drug resistant malaria parasite strains, the efficacy of an antimalarial drug demonstrated in one area may not be applicable to another. There was therefore, a need to find out the efficacy of AT as an alternative treatment for malaria in Tanzania. The study was carried out between the months of January and June, 1996.

Materials and Methods

The study was based at the Muheza Designated District Hospital (Teule) whose catchment area is holoendemic for malaria. There are high levels of multi-drug resistance of *P. falciparum*, particularly to CQ, SP and to a lesser extent, MQ. The study patients were selected from those seeking treatment from the hospital and its catchment health facilities.

Each of the potential patients was examined clinically and parasitologically by thin and thick Giemsa stained blood smears for malaria parasite identification and enumeration. Positive ones were interviewed to elicit age, a history of concurrent serious illness, and of ingesting antimalarial drugs within the past 14 days.

Those with a negative history were given a Dill-Glazko urine test for the presence of 4-aminoquinoline antimalarial drugs. Women of reproductive age were also interviewed for a history of concurrent lactation and missed menstrual periods of 5 weeks or more. In case of doubt regarding missed periods, a pregnancy test was employed to be certain. Only those aged 5 years and above, non-pregnant and non-lactating women who gave informed consent were registered for the study. Other blood samples were collected for the assessment of bone marrow, liver and kidney function tests. Blood Pressure and pulse rate measurements were taken and recorded daily and on each follow up visit.

Patients were randomised into two treatment groups, one for CQ and the other for AT. Both drugs were available as similar white tablets. This was advantageous for blinding patients for the treatment taken, and for those either carrying out clinical examinations or recording side effects. The patients' numbers, instead of names, were used for labelling specimens so as to blind the testing technicians for treatment administered to the patient and for the point along the study period. The identification of the patients by treatment was only known by the nurses who were the only ones administering the drugs. Although there was a chance to break the identification code to facilitate treatment of severe side effects or deteriorating illness, it was to be broken during data analysis.

AT was administered as tablets each containing 50 mg of the active ingredient. The calculation of the daily doses were based on the patients' body weights, given at 3.2 mg/kg on the first day, and 1.6 mg/kg on the following four successive days. CQ was also given as tablets each containing 150 mg base, and was administered at a dosage of 10 mg/kg on the first two days, followed by 5 mg/kg on the third day. Patients were admitted in hospital for 7 days, and thereafter, followed up as out-patients on days 14, 21 and 28. During the follow up, clinical assessment and parasitological examination of blood slides were performed, and blood samples for physiological function tests were collected and examined.

Results

A total of 106 patients, 54 for CQ and 52 for AT were analysed. AT had a rapid, progressive and significant effect as by day 3 it already attained 23.5% parasite clearance in contrast to only 5.6% scored by CQ. Throughout the follow up period up to 28 days, AT recorded not only consistently rising but also highly significant parasite clearance rates, reaching a peak of 92.2% on day 7 compared to 57.7% achieved by CQ. Cure rate as observed on day 28 was higher in the AT group (79.5%) than in those treated with CQ (27.9%). However, there was no difference in the clinical response noted between these two drugs. In addition, both drugs

showed high rates of recrudescence. The only side effects recorded were itching and dizziness. Two patients on CQ group and one on AT complained of itching, and only one in the AT group reported to have dizziness. There were no marked abnormalities noted in the physiological function tests except for a few who showed some decrease in the total white cell count, particularly in those treated with CQ.

Discussion

This clinical trial has demonstrated that the two drugs were well tolerated, with AT being the better off. The only elicited side effects were itching and dizziness, both of which were mild, transient and resolved spontaneously. The physiological function tests showed that only leucopenia and reticulocytosis could possibly be associated with the interventions since the post-treatment rates increased beyond the pre-treatment levels, more so in patients treated with CQ. This therefore, shows that AT was virtually without adverse effects as reported elsewhere (Myint, P.T. and Shwe, T., 1986; Karbwang *et al.*, 1992).

For both treatment groups, the post-treatment prevalences for each of the malaria related manifestations decreased dramatically and consistently to rates well beyond the pre-treatment levels. The similarities in the clinical response probably indicate an equal pharmacological action. Nevertheless, AT was far superior to CQ in terms of parasite clearance and cure rate as found in other studies done in Southeast Asia (Karbawang *et al.*, 1992). AT could provide a good alternative treatment for malaria in Tanzania. The main problem with it however, seems to be related to the rate of recrudescence. For it to be more effective, and for preventing it from developing resistance in the near future, it should be combined with another antimalarial drug to give it a synergistic effect.

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