THE RESPONSE OF *PLASMODIUM FALCIPARUM* TO CHLOROQUINE, AMODIAQUINE AND SULFADOXINE/PYRIMETHAMINE IN MUHEZA, NORTH-EASTERN TANZANIA

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ABSRACT: A randomised clinical trial was conducted in Muheza district, Tanga, Tanzania to evaluate the efficacy of chloroquine (CQ), amodiaquine (AQ) and sulfadoxine/pyrimethamine (SP) in treating malaria. 118 children aged between 5 and 14 years who had uncomplicated falciparum malaria were randomised into 3 treatment groups. CQ and AQ were both given at a dosage equivalent to 25 mg base per kg of body weight, over 3 days. Dosage for SP was determined by calculating 25 mg of sulfadoxine per kg, and given as single doses. AQ attained a 100% clinical and parasitological clearance on days 3 and 7. A few of the patients on SP had persistent symptoms and a 95% parasite clearance during the first week of treatment. Over half of those on CQ had persistent symptoms, and 35% of them were still positive for malaria parasites during the first 7 days of treatment. On follow up through 28 days, CQ achieved a cure rate of only 25.6% in contrast to 67.6% and 63% scored by AQ and SP respectively. It seems CQ is no longer effective enough to deserve to continue being the first line drug for the treatment of malaria. AQ could be a better choice to replace CQ as the first line drug.

Introduction

Malaria is still the most important parasitic disease in the tropics and sub-tropics. It ranks high among the major causes of morbidity (WHO, 1990), particularly in young children and pregnant women (Mendis and Carter, 1994), causing death of between 1 and 3 million people in these two age groups in sub-Saharan Africa (Stuerchler, 1989). The disease is the leading cause for out-patient attendances, hospital admissions and hospital reported deaths in Tanzania.

In practical terms, malaria control depends very much on proper case management. The emergence of resistant strains of *Plasmodium falciparum* to the first line drug, chloroquine (CQ), and to some degree lack of the second line and reserve drugs has seriously hampered the prospects of malaria control. For quite some time now CQ has been showing very dissatisfying response almost all over the world. This awkward situation has forced some countries to review their treatment policies. As a consequence, Malawi chose SP as the

first line instead of CQ (Bloland et al, 1993). Premji et al. (1994) reported a CQ resistance of as high as 50% in school children in a coastal vilage in Bagamoyo district, Tanzania. In Muheza district, Tanzania SP is used as the first line for the treatment of uncomplicated malaria in children below the age of 5 years.

This study was carried out between the months of May and June 1995, and was intended to re-examine the response of *P. falciparum* to CQ , AQ and SP and see if it was still rational to rely on CQ as the standard treatment for malaria in our country, or if it was necessary to make a change in our treatment policy. And if we think we need to make any changes, based on the therapeutic efficacy, which between AQ and SP, the possible candidates, could effectively replace CQ? This paper, therefore, analyses the clinical and parasitological ability of these three drugs.

Materials and Methods

Study Site, Population and Data Collection

The study took place in Tongwe dispensary and Mpapayu village in Muheza district where malaria is intense and perennial, with peak transmission during the rainy seasons, particularly so at the end of the season. Over 90% of the malaria infection is caused by *P. falciparum*. Like elsewhere, in the country, resistance of this malaria parasite species to CQ and other antimalarial drugs exists in the district.

Children aged between 5 and 14 years inclusive, who reported to either Tongwe dispensary or the treatment centre established at Mpapayu village seeking medical services, formed the study group. those with signs and symptoms related to malaria were screened by thick and thin blood films for parasite detection and identification. Patients who were found positive for *P. falciparum* only were registered after giving informed verbal consent. Qualifying patients were randomised into 3 treatment groups with respect to the drugs being tested. CQ and AQ were both given at 25 mg/kg over 3 days. SP was administered in a dosage based on sulfadoxine at 25 mg/kg and given as single doses. Drug administration was done under the supervision of the investigating team. Patients were followed up on days 3,7,14,21 and 28.

Results

Of the initial 126 patient registered, 118 completed the study. Clinical assessment on day 3 of treatment showed marked improvement in all the 3 groups. However, there were a few patients in the CQ group who had persistent symptoms, and one patient in the SP group with vague abdominal complaints , but none at all in those treated with AQ who presented with any symptoms. Parasitological evaluation revealed corresponding findings whereby all patients (100%) treated with AQ had negative blood slides compared to 36 out of 38 (95%) and 30 out of 43 (70%) on SP and CQ respectively. Clinical and parasitological assessment on day 7 showed negative blood slides and no complaints in the group that received AQ, but recurrence of symptoms seemed to have been increased in the SP treated group, although the parasitological response remained unchanged. Over half of those on CQ had recurrence of symptoms, and 35% of them had positive blood slides. On follow up through 28 days it was observed that 67.6% of patients treated with AQ and 63% of those on SP had negative blood slides in contrast to only 25.6% on CQ. All levels of resistance (RI – RIII) were recorded in the CQ group. SP had resistance up to RII, but no resistance beyond RI were recovered in the AQ group.

Discussion

Tanzania is one of the East African countries where CQ resistance in Africa was first reported (Campbell *et al.*, 1979; Fogh *et al.*, 1979). Since that time the problem intensified in proportions and magnitudes. In this particular present study it was clearly shown that CQ resistance has reached a very serious level (74.44%) that requires an immediate action. The results have also shown that SP is running fast in the development of resistance, as it was noted that up to RII level of resistance was recorded in its group. On the other hand, AQ seems to have performed better than the two other drugs both clinically and parasitologically. Despite the fact that SP had a relatively good clinical and parasitological record, it does not appear to have a bright future. Clyde (1954) observed, a decline in the prophylactic efficacy of pyrimethamine in a local population, and later the existence of resistance was confirmed in clinical study around Muheza (Clyde and Shute, 1954). In a recent study, Ronn *et al.*, (1996) reported high level of resistance in SP in a village near Muheza town. It is a known fact that sulfa drugs are not very safe. The sulfa component of this drug combination can cause some very serious and fatal adverse reactions (Bjokman and Phillip - Howard (1991). Such reactions occur more frequently and more seriously (Steven - Johnson syndrome) in HIV positive than in HIV negative individuals. There are therefore, two anticipated problems if SP is recommended as the first line drug in Tanzania; firstly, there is high possibility for resistance to develop in SP very soon as there is already resistance in pyrimethamine. Again, experience has shown that increased therapeutic use can lead to the emergence of drug resistant strains (Ronn et al., 1996). Secondly, extensive use can result into an increase in the incidence of adverse reactions, particularly if we put into account the fact that HIV prevalence is increasing in our community.

It is obvious that AQ is not free from adverse reactions, but most of the side effects are either dose-related or have something to do with frequency or duration of therarpy as happens in prophylaxis. There are also some dangers of developing liver and bone marrow damage when AQ is used therapeutically if the rate of acquiring infection is high and the interval between clinical illnesses becomes short, like what happens in the endemic areas, in which case the drug would be

prescribed in short intervals as in prophylaxis. But if used properly and only for treatment (and not for prophylaxis), and if the therapeutic interval would not be too short, then AQ has no major problems. HENCE, AQ could be better than SP.

In view of the high levels of CQ resistance, continuing using it as the standard treatment of malaria increases the incidence of people at risk of malaria morbidity and mortality, particularly in the rural areas where CQ is probably the only available and dependable antimalarial drug. From the results of this study, therefore, it is obvious that a change of the first line drug is inevitable; and AQ appears to be the sound choice.

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