ABSTRACT

Malaria continues to be a major public health problem in Sri Lanka and it is well recognised that drug resistance is an important obstacle encountered by the National Malaria Control Programme. This study was carried out a) to determine the distribution of chloroquine resistant *P.falciparum* malaria in Sri Lanka, b) to evaluate a health education intervention to improve revisits of *P.falciparum* malaria patients, and c) to evaluate the efficacy, safety and tolerability of combination therapy using artesunate, sulphadoxine+pyrimethamine and primaquine in the treatment of *P. falciparum* malaria infections.

The study was carried out at 2 components. In the first phase of the 1st component of the study, a nationally representative sample of 900 *P.falciparum* patients was studied to estimate the incidence of chloroquine resistant *P.falciparum* malaria in Sri Lanka. The study was confined to nine malaria endemic districts excluding the districts of the North-East Province which were excluded due to the prevailing war situation. All patients were actively followed over a period of 21 days for recrudescences of parasitaemia using a modified version of the therapeutic efficacy testing protocol recommended by the WHO. Patients were followed up by performing microscopy on days 7, 14 and 21. RI, RII and RIII levels of resistance were defined as given by WHO. After obtaining the expected number of chloroquine resistant *P.falciparum* cases, it was estimated that 51% of *P.falciparum* infections were resistant to chloroquine in Sri Lanka in 1999. Among the resistant infections 70.6% were RI, while 11.5% and 17.9% were RII and RIII respectively. This estimate is considered an

underestimate as the test was an *in-vivo* test and the test procedure followed patients only for 21 days.

Associations between sensitivity status and selected socio-demographic variables were tested using chi-square tests, t-tests and logistic regression models. Resistant infections were more common in younger age groups (<25 years), those divorced, separated, widowed or single and in persons who were resident more than 10km from a medical institution. Only few patients had fever at the time of presentation. At follow up, patients with chloroquine resistant *P.falciparum* infection experienced less symptoms of clinical disease than during their primary infection. The majority of recrudescent infections presented with anorexia, myalgia, arthalgia and weakness which were not typical of malaria. Age, distance to the closest medical institution, bus fare per visit and economic loss were modeled using logistic regression.

Phase II of the 1st component of the study was carried out to determine the possible interventions to improve early diagnosis and treatment of chloroquine resistant *P. falciparum* infections. This phase was carried out in Anuradhapura district, comprised the implementation and evaluation of a health education package to improve follow up visits of *P. falciparum* patients. The health education package included the distribution of a leaflet (which contained health education messages) and an appointment card, and giving an educational talk to *P.falciparum* patients regarding the importance of follow up visits on day 7, 14 and 21. Four health areas in the Anuradhapura district was selected for the study based on the incidence of malaria and the incidence of *P.falciparum* in the past five years. Two

health areas received the intervention while the other two acted as a control. A total of 540 patients were studied with each group consisting of 270 patients. Patient follow up was on days 7, 14 and 21 was monitored at health institutions participating in the study.

At baseline, there were statistically significant differences in the characteristics of patients such as age, marital status, occupation, level of education, number of attacks of malaria during the past year, distance to the closest medical institution and economic loss to the patient for the initial visit to the medical institution between the intervention and control group. Follow up visits among the patients in the intervention group, as compared to the control group, was higher than in the control group on all 3 follow up days, i.e., on days 7, 14 and 21, however, only on day 14 was the difference statistically significant.

To identify factors associated with revisits, data from the two groups were aggregated for days 7 and 21 and for day 14, a stratified analysis, using the Mantel Haenszel chi square test, was done as there was a difference in the revisit rate between the intervention and control groups. Revisits in general were influenced by factors such as total monthly family income, economic loss to patients, distance to the closest medical institution and number of malaria attacks experienced by patients during the past year. In addition, on day 14, sex, marital status and level of education were also significantly associated with revisits.

Patients who had positive blood smear, on the average, had more symptoms of clinical disease as compared to patients who tested negative.

Although, it cannot be concluded that the intervention was as absolute success, it could be considered that the intervention was partially successfully in at least improving the revisit rate on day 14. The intervention carried out in this study is easy and cheap to duplicate in all malaria endemic districts.

The 2nd component of the study carried out in the Moneragala Base Hospital was a prospective study to assess the efficacy, safety and tolerability of combination drug therapy for *P. falciparum* infections. The combination included a single day course of a combination of sulphadoxine+pyrimethamine and primaquine, and a three-day course of artesunate. Thirty patients were followed over a period of 28 days. The asexual parasitaemia reduced significantly within 24 hours of administration of the drugs and cleared by day 7. The gametocytaemia reduced significantly by 48 hours of commencement of treatment and had cleared after day 7. The haematological and biochemical analysis were within normal limits before and after treatment. No adverse reactions were observed in the study. The combination therapy was well tolerated in the prescribed dosages and was found to be safe.

The findings of this study have far reaching implications for drug policy in the choice of antimalarials in Sri Lanka. The addition of an antimalarial such as artesunate that is quickly eliminated from the body will help in averting the predicted disaster of sulphadoxine+pyrimethamine developing resistance rapidly, should it be used alone as the first line of treatment.