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CHLOROQUINE VERSUS PYRIMETHAMINE/SULPHADOXINE IN THE TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA IN NORTHERN KENYA.
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CHLOROQUINE VERSUS PYRIMETHAMINE/SULPHADOXINE IN THE TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA IN NORTHERN KENYA

F. FALASCHI and L. ANSALONI

SUMMARY

The response of *P. Falciparum* to chloroquine (CQ) and pyrimethamine-sulphadoxine (PSD) *in vivo* was investigated in 173 indigenous uncomplicated malaria patients at Sololo Hospital, Moyale district in northern Kenya. All the patients were symptomatic and parasitaemic. They were divided in two age groups (children <10 years, adults >10 years). They were randomly assigned to receive either CQ or PSD standard treatment and then followed up at 7 and 14 days. In the child group, out of 91 patients enrolled, 65 (71.4%) completed the seven-day study; among these 38 (17 females and 21 males with mean age of 41.9 months) were treated with CQ and 27 (11 females and 16 males with mean age 39.1 months) with PSD. Parasites were significantly (p<0.001) more resistant to CQ (18/38, 47.4%) than PSD (0/27, 0%). In the adult group, out of 82 patients enrolled, 54 (65.9%) completed the 7-day-study, and among these 27 (10 females and 17 males with mean age of 22.5 years) were treated with CQ and 27 (11 females and 16 males with mean age of 23.2 years) with PSD. Parasites were significantly (p=0.01) more resistant to CQ (7/20, 25.9%) than PSD (0/27, 0%). Overall, considering the 119 patients who completed the follow-up, the resistance of *P. falciparum* was significantly higher (p<0.001) to CQ (25/65, 38.5%) than to PSD (0/54, 0%). Out of the 94 patients with negative slide at day 7, fifty seven came at the control of the day 14 (30 children and 27 adults). Among them, 22 were in CQ group and five were found positive (22.7%), while the 35 patients in PSD group all tested negative (p=0.006). The resistance to CQ in the children group was 25% (p=0.05) and 20% in the adult group (p=0.13). We conclude that the significant parasitological resistance to CQ in the area under study questions the continued use of CQ as first line antimalarial treatment. On the contrary, PSD can still be considered a very effective drug against *P. falciparum* in northern Kenya.

INTRODUCTION

The first chloroquine (CQ) resistant *P. falciparum* malaria in Kenya was documented in non-immune tourists in 1979, and thereafter in local Kenyan children and adults in 1983 and 1984 (1-2). Since that time, CQ resistance has become a serious health problem in Kenya and throughout East Africa(3-6). Our objective was to determine the degree of CQ resistance in an area in northern Kenya from where data is scarce and to compare this with the efficacy of pyrimethamine/sulphadoxine (PSD).

MATERIALS AND METHODS

The study was carried out at Sololo Hospital, a 100-bed rural hospital in the District of Moyale. The area is located at the base of the Ethiopian plateau with moderate seasonal rainfall and mesoendemic seasonal (April-July; November-January) malaria (7-8). Between 5th of April and 20th of July 1995, 202 patients were diagnosed to have *P. falciparum* malaria through a positive thick film slide. Among these, 29 were excluded for complicated malaria (n= 5), antimalarial treatment in previous week (n=13) or pregnancy (n=11). The remaining 173 patients were enrolled and divided in two age groups: 91 children (< 10 years) and 82 adults (>10 years). The patients in both age groups were randomly assigned to CQ (25 mg/kg in 4 doses, first dose 10 mg/kg, second dose after six hours and following after 24 and 36 hours 5 mg/kg) or to PSD (tablet of 500 sulphadoxine + 25 pyrimethamine: 1/2 tablet every 10 kg, maximum three tablets). During the study period the cost for one CQ treatment for an adult was six Kenya shillings (at a cost of one CQ tablet 0.6 Kenyan shillings and the composition of one full treatment 10 tablets), as compared to 6.6 Kenya shillings for PSD (at a cost of one PSD tablet 2.2 Kenya shillings and the composition of one full treatment three tablets). At the end of the random sampling, 88 patients (47 in the child group and 41 in the adult group) were treated with CQ and 85 (44 in the child group and 41 in the adult group) with PSD. The patients or their caretakers were accurately explained how to take the treatment and instructed to repeat any dose which was followed by vomiting in less than one hour. The parasitaemia was measured on day 0, 7 and 14 by counting the number of ring forms per 100 leucocytes and by determining the white blood cell count. The parasitaemia was determined in some patients between day four and day six in case of clinical worsening or lack of substantial improvement. A treatment failure was defined as a positive slide after day four and was treated with a second line drug. No measures were taken to blind the patient or the investigators, but the laboratory technicians, although

theoretically they could have access to that information, were substantially unaware of the treatment group to which the patient was assigned. Data analysis was performed by comparing proportions using the Chi square test (or Fischer's exact test when appropriate) and ANOVA for means in the EPI Info 6.02 package.

RESULTS

Out of 173 patients enrolled in the study, 119 (68.8%) returned for slide control between day 4 and 7, sixty five out of 91 (71,4%) in the child group and 54 out of 82 (65,9%) in the adult group. The proportion of defaulters in the two treatment groups and the relative risks with 95% Confidence Intervals (CI) are shown in Table 1.

Table 1

Proportion of defaulters and the relative risks (RR) with 95% Confidence Intervals (CI) in the two treatment groups

	Proportion of defaulters with CQ	Proportion of defaulters with PSD	RR	95% CI
Child group	0.23	0.62	2.02	1.01 - 4.05
Adult group	0.51	0.51	1.00	0.55 - 1.82
Total	0.35	0.57	1.40	0.89 - 2.19

No significant difference regarding sex, mean age and mean parasitaemia was detected between the group of defaulters and the group followed up at day four and seven. Baseline characteristics of the 119 patients who came for control between day four and seven divided in the two treatment groups are reported in Table 2.

Table 2

Baseline characteristics of the 119 patients who came for control between day 4 and 7 in the two treatment groups (SD=standard deviation)

	CQ	PSD	p value
Total group			
Number	65	54	
Male/female	38/27	32/22	0.92
Mean age, years (SD)	11.5 (12.7)	13.2 (14.5)	0.51
log parasitaemia (SD)	3.9 (0.7)	3.9 (0.7)	0.68
Child group			
Number	38	27	
Male/female	21/17	16/11	0.95
Mean age, months (SD)	41.9 (31.2)	39.0 (34.7)	0.73
log parasitaemia (SD)	4.1 (0.7)	4.0 (0.7)	0.77
Adult group			
Number	27	27	
Male/female	17/10	16/11	1.0
Mean age, years (SD)	22.6 (13.0)	23.2 (14.7)	0.86
log parasitaemia (SD)	3.6 (0.6)	3.9 (0.7)	0.12

Among the 65 patients treated with CQ, 25 (38.5%, 95% CI 26.7%-51.4%) were still positive at day 4 to 7 slide control whereas none was positive in the group treated with PSD: the difference in efficacy of the two drugs is statistically significant ($p<0.001$). No significant difference regarding sex distribution, mean age and mean parasitaemia was detected between the group of patients with positive and negative slide at day 4 to 7. Splitting the day 4 to 7 results by age group the resistance of *P. falciparum* to CQ in the child group was 47.4% (95% CI 31.0%-64.2%; $p<0.001$) and in the adult group 25.9% (95% CI 11.1%-46.3%; $p=0.01$). These results are summarised in Table 3. The difference in sensitivity of *P. falciparum* to CQ in the two age groups was not statistically significant ($p=0.14$), although it suggested age could be a possible protective factor.

Table 3

Positive rate at four to seven day slide control in the two treatment groups

	CQ	PSD	p value
Total group Positive/TotalNumber (%)	25/65 (38.5)	0/54 (0.0)	<0.001
Child group Positive/Total Number (%)	18/38 (47.4)	0/27 (0.0)	<0.001
Adult group Positive/TotalNumber (%)	7/27 (25.9)	0/27 (0.0)	0.01

Out of the 94 patients with negative slide at day four and seven, 57 came at day 14 slide control (30 children and 27 adults). Among them, 22 were in CQ group and five were found positive (22.7%, 95% CI 7.8%-45.4%), while the 35 patients in PSD group all tested negative ($p=0.006$).

Table 4

Positive rate at 14 day slide control in the two treatment groups

	CQ	PSD	p value
Total group Positive/TotalNumber (%)	5/22 (22.7)	0/35 (0.0)	0.006
Child group Positive/Total Number (%)	3/12 (25.0)	0/18 (0.0)	0.05
Adult group Positive/TotalNumber (%)	2/10 (20.0)	0/17 (0.0)	0.13

No significant difference regarding sex distribution, mean age and parasitaemia was detected between the group of patients with positive and negative slide at day 14. The resistance to CQ in the child group (N=12) was 25% (95% CI 5.5%-57.2%; $p=0.05$) and in the adult group (N= 10) was 20% (95% CI 2.5%-55.6%; $p=0.13$), as shown in Table 4.

DISCUSSION

Our study shows how simple it is, even in a small rural hospital, to monitor *in vivo* resistance of *P. falciparum* to the most common drugs used in the therapy of malaria with a follow-up at the day 7 and 14.

The most evident draw back of our study is the

notably high dropout rate at follow-up, since we did not use any type of incentive. As shown in Table 1, although there is a slightly higher relative risk to dropout at the day-seven-control for the group treated with PSD, this is significant only in the child group. Furthermore, there were no significant differences regarding sex, age and mean parasitaemia between the group of defaulters and the group followed up at day four and seven. This difference in the relative risk could be explained by the better performance of PSD over CQ. Hence the 38.5% resistance of *P. falciparum* to CQ could be an overestimation: however, using as denominator even the complete group of 88 patients treated with CQ, instead of the 65 who actually came for control between day 4 and 7, the resistance rate of *P. falciparum* to CQ still remains 28.4%. In addition, the performance of CQ becomes even less effective, considering that we found a further 22.7% resistance of *P. falciparum* to CQ in the group of patients that came at day 14 slide control.

Several reports already have shown the high resistance rate of *P. falciparum* to CQ in many areas of Kenya, mostly in the coastal (9-10) and western regions (11), and more recently in areas of "highland malaria" (12). Our report confirms for the first time, to our knowledge, that even in northern Kenya the resistance of *P. falciparum* to CQ is widespread.

On the contrary, many authors have stated that PSD is still very effective in Kenya (10-13), although sporadic cases of the resistance of *P. falciparum* to these antifolate drugs had already been reported (14). Even our randomised trial verifies that PSD is significantly more efficacious in the treatment of *P. falciparum* malaria than CQ. Furthermore PSD at practically the same cost of CQ, has the advantage of a single dose administration which could improve the compliance of the patients; the risk of rapid development of resistance after wide use of this drug in the area would be limited by the strict seasonality of the malaria and could be easily monitored using simple studies such as this.

We conclude that: (i) simple *in vivo* systems of monitoring the chemosensitivity of *P. falciparum* to the commonly available antimalarial agents should be set up periodically even in small, rural hospitals, in order to make current the knowledge about this health matter in the different regions of the country and to rationalise drug use; (ii) in northern Kenya the therapeutic use of CQ as monotherapy in *P. falciparum* malaria is questionable and should be replaced by more efficacious drugs, such as PSD, or combination treatment.

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