Mem. Inst. Oswaldo Cruz, Rio de Janeiro, Vol. *87*, Suppl. III, 265-269, 1992

THE TREATMENT OF FALCIPARUM MALARIA IN CHILDREN WITH HALOFANTRINE SUSPENSION

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Malaria treatment of children is particularly difficult because of the absence of palatable suspensions for young children. Halofantrine hydrochloride is available as a suspension which is both palatable and simple to administer, and has been studied in a number of trials in the past 5 years.

Children (331) ranging from 4 months to 17 years of age (mean 4.7 years) were treated with the 5% suspension using various dose regimens and 364 children ranging from 4 months to 14 years of age (mean 5.7 years) were treated with the 2% suspension 6 hourly for 3 doses. Using the 3-dose regimen there were only 2/462 (0.4%) who failed to clear the initial parasitaemia. Recrudescence occurred in 28/367 (7.6%) children with evaluable follow up data. The mean parasite clearance time in this group was 57.1 h (n = 417) and the mean fever clearance time was 50.9 h (n = 325). Symptoms related to malaria cleared rapidly following treatment generally by 24-48 h post treatment.

Side effects possibly related to treatment were uncommon but were similar to those reported in adults. The frequency of diarrhoea and abdominal pain was lower than that seen in adults and was also less frequent following multiple doses and the use of the more dilute suspension.

Since there was evidence that the majority of recrudescences were seen in younger children or those living in areas with low or seasonal transmission it is recommended that a further course of treatment 7 days later is given to these patients to prevent recrudescence.

Halofantrine suspension appears to be effective and well tolerated in children and is a useful addition to the drugs available for the treatment of paediatric malaria.

Key words: *Plasmodium falciparum* – malaria – treatment – halofantrine – children

Malaria treatment in children is made particularly difficult because of the absence of palatable suspensions for young children and the need to break adult tablets to provide a weight titrated dose. A suspension of halofantrine hydrochloride (Halfan SKF) is available which is both palatable (although flavourless, the suspension is flavoured to improve acceptance in young children) and easy to administer. The suspension has been studied in a large number of trials over the last 4 years.

Early development studies in children with acute malaria were performed using a 5% w/v suspension. When this formulation was originally developed it was considered that a single dose of halofantrine would be sufficient to treat young children, and the volume to be administered were therefore manageable. However it was found in both adults and children that a regimen using approximately 8 mg/kg per dose for 3 doses 6 hourly (total dose 24 mg/kg) gave better clinical results. The use of a divided dose regimen with the 5% suspension required the administration of doses which were multiples of 1 ml for each dose. While this was practical for use in clinical trials, it was clearly not for general use. The suspension was therefore reformulated to 2% w/v without significant changes in excipients. This enabled the use of

doses of 5 ml and 2.5 ml and multiples thereof using a graduated spoon. Such doses were easier to measure and the suspension had the added advantage of flowing better, thus reducing the likelihood of underdosing.

We report here the accumulated experience of treatment of children with acute malaria treated with both 5% and 2% suspension.

MATERIAL AND METHODS

Children with acute malaria weighing less than 40 kg were treated with suspension in 19 studies, 8 using the 5% suspension at various doses and 11 using the 2% suspension all using an 8 mg/kg dose given 6 hourly for 3 doses (Fig. 1). The studies were conducted according a core protocol on children who had mild to moderate parasitaemia and were generally symptomatic. Parasitaemias were followed until clearance and then at 7, 14, 21 and 28 days post treatment. Fever was similarly documented. Symptoms and signs occurring before and after treatment were recorded and the time to disappearance noted. Laboratory tests (haematology, biochemistry) were performed before and regularly during the post treatment follow up, but the range of tests performed varied because of differing availability and the varied ages of the children studied.

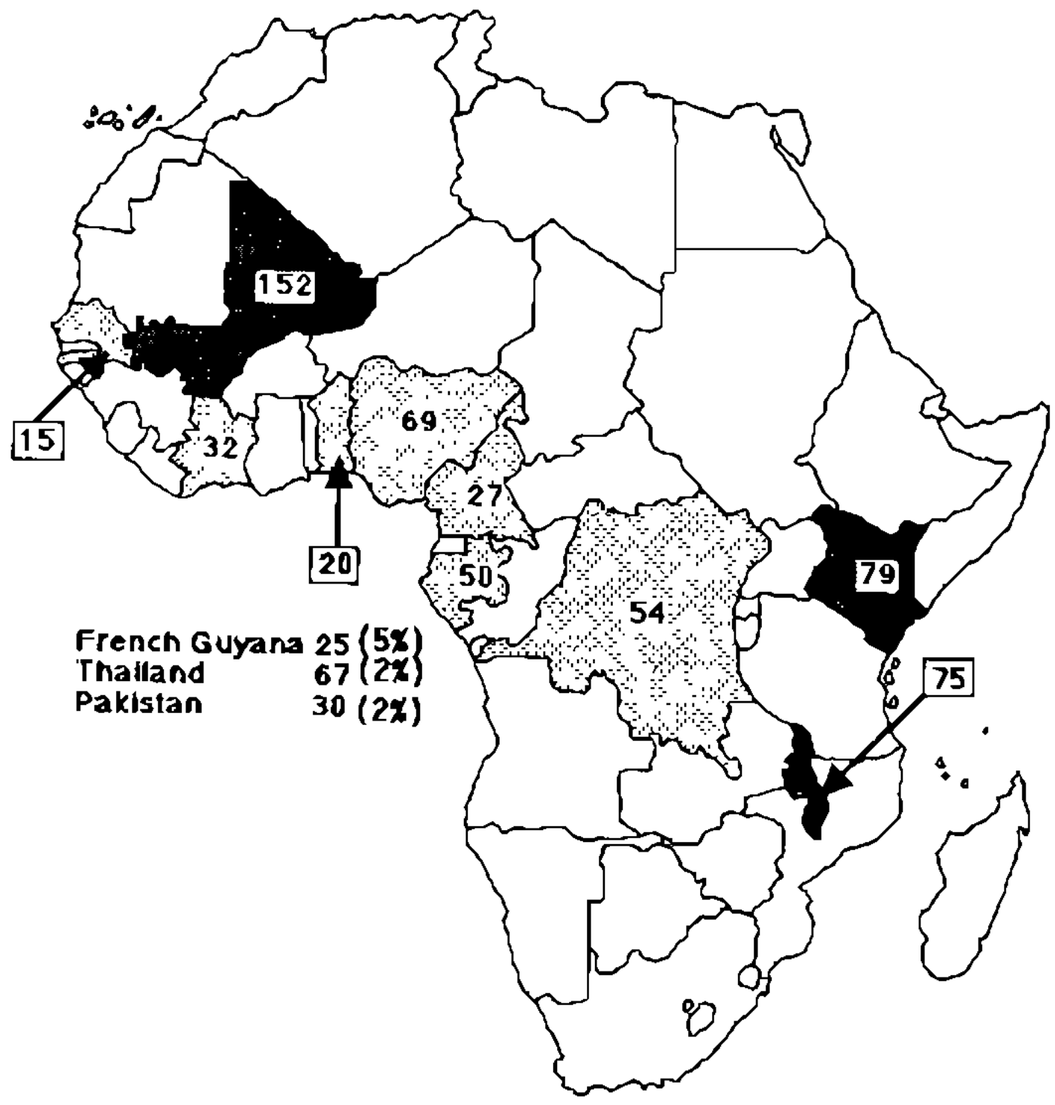

Fig. 1: sites and number of children investigated. Dark: 5% suspension. Light: 2% suspension.

RESULTS

Demography – Data is presented from 331 children in 8 studies using 5% suspension and 364 children in 11 studies using 2% suspension. All patients who received 2% suspension were treated using an 8 mg/kg dose 6 hourly for 3 doses initially, and in one study 16 of the children received a second course of treatment 7 days later as part of the protocol. 117 patients treated with 5% suspension received a single dose of 16 mg/kg, 90 patients were treated with two doses of 10 mg/kg and 124 were treated with 3 doses of 8 mg/kg 6 hourly. The details of the children treated with the two demographic formulations is summarized in Table I.

Efficacy – The outcome of treatment of *Plasmodium falciparum* malaria is summarized by dose frequency and suspension concentrations in Table II. In this table the number who treatment failed during the first 7 days, were lost to follow up before or after clearance of parasitaemia, recrudesced after clearance or were parasite free at the end of follow up are presented. With single doses, the initial failure rate was relatively high, and the majority came from one study in Malawi where a number of very small children with limited immunity were included. Both initial failures and recrudescence in this study were shown

TABLE I

Demographic details of study population

	5% suspension	2% suspension
Number of studies	8	11
Number of patients	331	364
Sex ratio M/F	171/160	201/163
Mean age (years)	4.73	5.71
Range	0.3-17.0	0.3-14.0
Past malaria	273	275
Mean weight (kg)	15.8	17.4
Range	5.5-58-0	5.5-45.0
Mean dose (mg)	312	509

TABLE II

Summary of treatment of *Plasmodium falciparum* malaria in children

Doses/Day		Number of studies	Total	Treatment failure	Lost to follow up	Evaluable patients	Recrudesced	Cured
5%	1	3	115	5 (4.3)	4 (3.5)	106	12 (11.3)	94 (88.7)
5%	2	2	90	0 (0)	1 (1.1)	89	5 (5.6)	84 (94.4)
5%	3	4	122	1 (0.9)	4 (4.5)	116	12 (10.3)	104 (89.7)
2%	3	11	340	1 (0.3)	46 (13.5)	293	16 (5.5)	277 (94.5)

TABLE III

Mean parasite and fever clearance times (hours) in children

Dose	Parasite clearance time		Fever clearance time	
	Number	Time	Number	Time
5% x 1	95	48.8 (24-168)	15	41.1 (10-108)
5% x 2	90	42.9 (24-96)	–	–
5% x 3	82	54.3 (24-96)	38	34.6 (24-144)
2% x 3	335	57.8 (12-168)	287	47.4 (4-168)

to correlate with age, being highest in the youngest children. With a 2 dose regimen there were no initial failures, and a low rate of recrudescence. However these studies were performed in older children, many of whom had very low parasitaemias and were asymptomatic. The results from the 5% suspension, 3 dose studies appear to be worse that the 2 doses studies, but the populations were younger, with higher parasitaemias and significant symptoms. Since, as with the Malawi study, there were age related failures, it was proposed that very young children should be retreated after 7 days.

In the 2% suspension studies there was only one patient who failed to clear their parasitaemia within the first week post treatment, while 2 were lost to follow up before parasite clearance. In 3 studies there were a large number of patients who failed to complete follow up according to protocol, although they were clear parasitologically at tthe time of the last visit, usually at 14 or 21 days. Overall there were 16 falciparum infections that recrudesced during or at the end of follow up, half of these coming from a single study in Thailand. It is possible that these were reinfections rather than recrudescences as the patients were not maintained in a malaria free environment. The efficacy following parasite clearance was 94.5% in those patients who were evaluable.

Only 4 children with *P. vivax* infections were treated with 5% suspension, there being 2 cures and 2 recrudescences. There were 24 children treated with the 2% suspension, 11 of whom were lost to follow up, with 10 defaulting after parasite clearance. Of the 13 evaluable, 3 recrudesced at 28 days, and 10 were parasitologically clear.

In Table III the parasite and fever clearance times are compared. The data is comparable for the two formulations. Range minima are accurate, but the maxima are dependent on the timing of visits. Thus some very long clearance times are recorded as these represent the next visit after clearance which may be up to 4 days later (i.e. no clearance on day 3 but next visit at day 7 therefore clearance = 168 h. However parasitaemia is presumed to have cleared between day 3 and day 7). Means and range maxima are therefore likely to be overestimates.

Safety – For comparisons of clinical safety, the symptoms present at the time of treatment and those occurring at any time during the follow up are compared (Table IV) for the two formulations.

For the group receiving 5% suspension, it will be noted that pre-treatment symptoms are less frequent when compared with the 2% suspension group. This results from a number of studies where patients had low parasitaemias and were generally asymptomatic. The post treatment events represent those which may possibly be drug related. However some may be due to continuing evolution of malaria symptoms during the first 2-

TABLE IV

Comparison of presenting symptoms and post treatment events in children receiving halofantrine 2% (n = 364) or 5% (n = 331) suspension

Event	5% suspension				2% Suspension			
	Presenting symptom		Post treatment event		Presenting symptom		Post treatment event	
	n	%	n	%	n	%	n	%
Fever	108	32.6	11	3.3	306	84.1	7	1.9
Vomiting	47	14.2	14	4.2	89	24.5	13	3.6
Headache	38	11.5	6	1.8	124	34.1	5	1.4
Coughing	36	10.9	46	13.9	9	2.5	14	3.9
Abdominal pain	28	8.5	15	4.5	86	23.6	12	3.3
Diarrhoea	20	6.0	31	9.4	34	9.3	9	2.5
Rigors	20	6.0	1	0.3	110	30.2	2	0.5
Nausea	18	5.4	1	0.3	40	11.0	3	0.8
Pallor	16	4.8	4	1.2	112	30.8	7	1.9
Pruritus	11	3.3	8	2.4	8	2.2	5	1.4
Jaundice	6	1.8	3	0.9	15	4.1	1	0.3
Dizziness	4	1.2	1	0.3	28	7.7	3	0.8
Rash	3	0.9	10	3.0	1	0.3	10	2.7
Palpitation	0	–	0	–	28	7.7	2	0.5
Anorexia	0	–	0	–	13	3.6	1	0.3
Convulsions	1	0.3	0	–	5	1.4	1	0.3

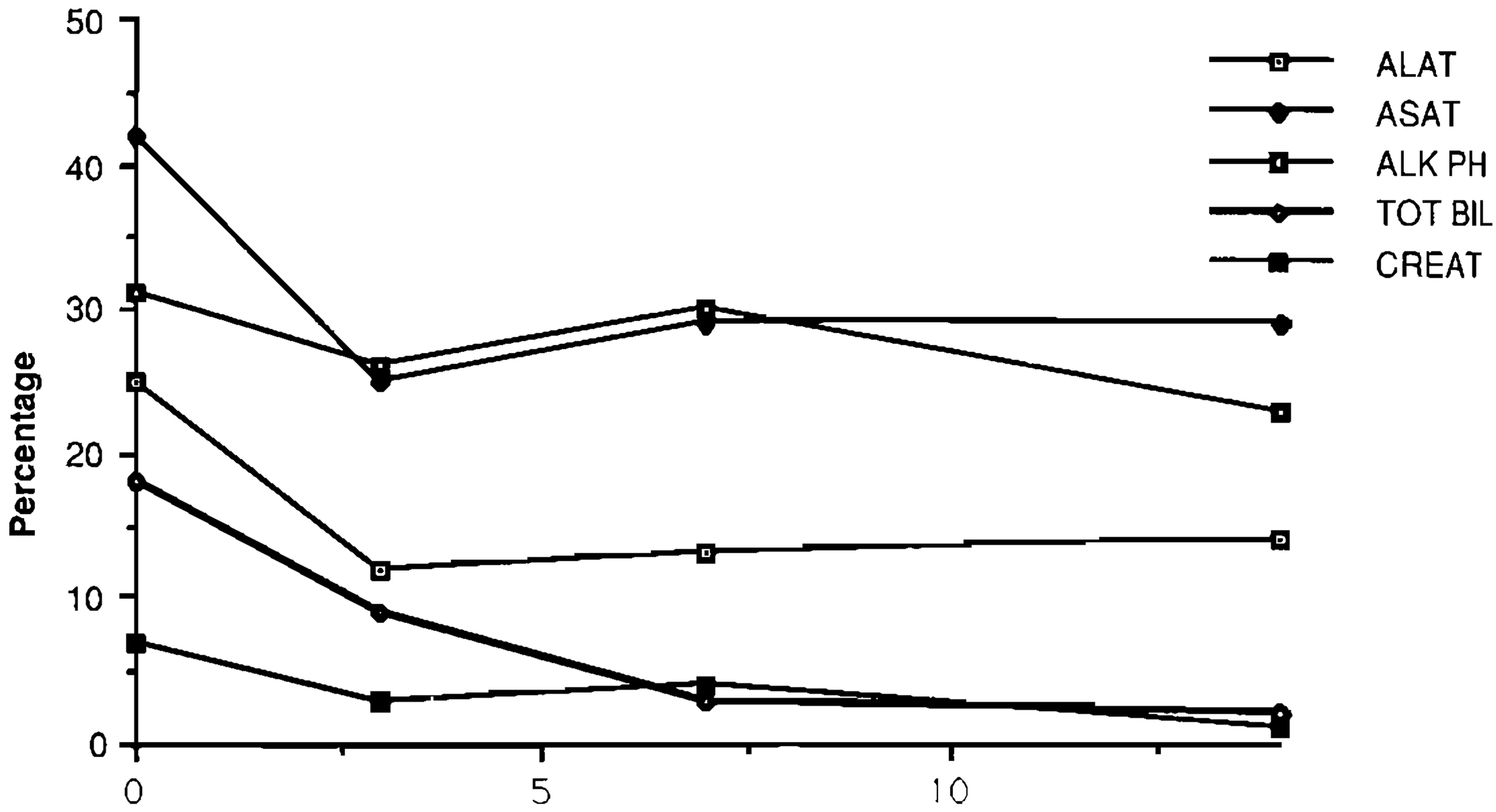

Fig. 2: percentage abnormal biochemistry values following halofantrine treatment in children.

3 days. Of particular interest is the lower frequency of abdominal pain and diarrhoea in the 2% group compared to the 5% group. Cough post treatment was the commonest event post treatment in both groups and probably represents background upper respiratory infections circulating in the population. Mucocutaneous events (rashes, pruritus) are commoner in the 2% suspension group which may be accounted for by the larger number of West African patients in the series.

Children entering the studies were clearly anaemic (Table V) before treatment. Unlike adult populations the reduction in red cell parameters

TABLE V

Changes in haematology parameters in children

Test	0	3	7	14	21	28
Haemoglobin (g/dl)	9.9	9.8	10.0	10.5	10.8	10.7
Haematocrit (%)	31.3	30.9	31.4	32.9	33.0	33.3
Red cells (million)	3.7	3.8	3.7	4.0	4.2	4.3
White cells (1000)	8.6	7.7	8.9	8.7	9.2	9.6
Platelets (1000)	195	218	265	263	263	300

in the first few days after treatment were not as pronounced, and recovery to pre treatment levels was more rapid, with significant increase occurring beyond day 7. White cell counts were essentially unaffected, and platelet counts showed the expected rises after treatment. Improvements in the number of abnormal values in the biochemical tests performed (Fig. 2) were clearly apparent within the first 3 days of treatment.

DISCUSSION

A substantial number of children aged from 4 months upwards have been studied for both safety and efficacy of suspension formulations of halofantrine. Although two different strengths have been used in these studies, and the groups studied are not entirely comparable it is clear that using the same dosage regimen, there is very little difference between the formulations. Differences are much more apparent between the different dose regimens with the 5% suspension.

Despite the similarity of results, there are clearly benefits in dosing simplicity with the 2% suspension which is easier to measure, and thus ensures accurate dosing. Examination of the safety aspects of the two strengths seems to indicate a benefit for the less concentrated suspension, with fewer gastrointestinal side effects. Overall however the accumulated data show that, in children of all ages, halofantrine is extremely well tolerated, without significant vomiting due to the absence of a bitter taste. It is therefore to be expected that compliance in children will be greater, despite the multiple dose regimen, and more consistent clinical response obtained through completion of treatment.