

Halofantrine Treatment of acute Plasmodium falciparum malaria in infants and young children

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Introduction

Malaria in very young children is a major therapeutic challenge in highly endemic areas where initial infection can occur in the first few months of life. Because active immunity has not begun to be established, infants are most at risk from falciparum malaria, and it has been estimated by the World Health Organisation that up to 10% of all infant mortality in Africa is directly or indirectly attributable to malaria. The rapid progression of symptoms from patency to severe and complicated malaria means that the time for intervention may be very short, and effective and appropriate antimalarial drugs are frequently in short supply. Added to this, malnutrition and other illnesses may accelerate the process, and in recent years drug resistance has further complicated the picture.

The therapeutic options for the treatment of very young children are very limited. In the early stages of malaria oral preparations may be used. However, oral chloroquine suspension is extremely bitter and poorly tolerated in infants, and in many parts of the world is now of limited efficacy because of drug resistance. In general suspension formulations of other anti-malarials commonly used in adults are not available. Breaking or powdering of tablets or oral use of parental preparations is therefore often employed to overcome the problem, especially for very young children. Such use, although necessary, is not ideal as the drugs are either not being used in the manner for which they were developed, or inaccurate dosing may occur. Halofantrine is a new antimalarial, unrelated chemically to other drugs in use. It has been possible to produce a palatable suspension without a significant after taste which has been shown to be effective in several studies of paediatric malaria (6, 7, 9). In these studies and others as yet unpublished some children under two years of age have been included, and it is now possible to analyse this subset of data in detail.

Material and methods

All studies were conducted to the same basic protocol according to the provisions of the Declaration of Helsinki, although technically all children included in this review should have been excluded from study protocols on grounds of age. Children were all parasitaemic with asexual *P. falciparum* parasite counts ranging from 1000 - 250,000/ μ l, but were not necessarily symptomatic. They were excluded if there was evidence of complicated malaria, significant other diseases or infections requiring treatment, a history of drug intolerance or significant dehydration requiring fluid replacement. Children, following a physical examination and granting of informed consent by parents or guardians, were treated initially as inpatients with halofantrine suspension, 8 mg/kg body weight, 6 hourly for 3 doses. Repeat parasite counts were performed daily until clearance of parasitaemia and then on day 7, 14, and where possible at 21 and 28 post treatment. Temperatures were measured at least twice daily until

normal ($< 37.5^{\circ}\text{C}$) for at least 24 hours and then at each follow up. Symptom review was undertaken daily until discharge and at each subsequent follow up. Only limited haematology and biochemistry studies could be performed on a few children owing to their small size and the availability of appropriate laboratories. Data on all children less than 2 years of age were extracted from the SmithKline Beecham clinical trial data base and analysed descriptively. This age cut off was chosen as it, or the limit of 10 kg body weight, is the lower limit covered by the current prescribing information for halofantrine.

Results One hundred and forty eight children under two years of age were identified for inclusion in this evaluation. There were 79 females and 69 males, aged from 4 to 23 months (mean 13.7 months). Their weights ranged from 5.2 kg to 20 kg (mean 8.6 kg, median 7.7 kg). There were two clear outliers with weights of 14.6 and 20 kg, but no explanation for these data could be determined. Only 30 of the children weighed 10 kg or more.

Despite their age, malaria exposure was high; of 122 infants with data recorded, 96 (78.6%) had a positive history. Of these, 27 had no history of malaria in the previous 6 months, but 33 were recorded as having malaria once, 19 twice and 15 infants had 3 or more attacks.

Following treatment with a dose of 8 mg/kg for 3 doses every 6 hours, only one patient, a child of 7 months weighing 7.3 kg remained parasitaemic at day 7. This child had an initial parasitaemia of 7742/ μl which fell slowly so that by day 2 it was reduced by about 50%, and by day 5 had fallen to 273/ μl . However, at day 7 it had risen dramatically to 36,960/ μl . The child was withdrawn and treated with quinine.

The majority of children were followed up to day 14 post treatment. During the period 7 - 14 days 4 of 124 evaluable children (3.2%) had reappearance of parasitaemia. Since the majority of studies were performed in transmission areas, and it was not possible to ensure a mosquito (and therefore malaria free) environment, further follow up was limited to a few individuals. In the period 14 - 21 days one parasitaemia occurred in 33 evaluable patients, and in the next 7 days a further 4 children became parasitaemic. It is, however, not possible in this group to determine whether these were true recrudescences or reinfections. In the whole population the mean fever clearance time was 46.8 hours ranging from 4.0 - 336 hours (69 patients with data) and the mean parasite clearance time was 69.3 hours (range 12.0 - 168 hours).

Further evaluation of the pattern of parasite clearance was undertaken. In figure 1 the proportion of patients clear of parasites at each time point is shown. The median of 42 hours, when compared to the mean, indicates that a higher proportion of the population clear early, and the mean is inflated by a few late clearances. Time to clear parasitaemia is a somewhat artificial parameter, since very low parasitaemias are difficult to detect, even for the very experienced. The rate of fall of the initial parasitaemia (fig. 2) is more important, since it is an expression of the response to treatment, and of greater clinical importance than the time taken to completely clear parasitaemia. A 50% fall (PC_{50}) was calculated at 10 hours, PC_{90} at 16 hours and PC_{99} at 32 hours.

Although clinical symptoms are difficult to evaluate in infants, fever was reported by parents in 121 children (81.7%) prior to treatment (tab. 1). Other symptoms occurred in less than 25% of the population. Symptoms other than pallor and cough cleared rapidly with over 80% resolved by day 2 post treatment. Substantial numbers of children still had pallor or cough beyond day 7 of follow up. It is likely that these symptoms were related to other underlying pathology rather than malaria infection.

Symptoms post treatment were reported relatively rarely, only cough and diarrhoea occurring in over 5% of children (Tab. 2). The day of appearance of the three commonest symptoms was evenly distributed over the first 7 days post treatment. All these events were mild and self limiting, not requiring any intervention. Only the two cases of stomatitis, and the single case of rash were prolonged, lasting for 3 - 4 days.

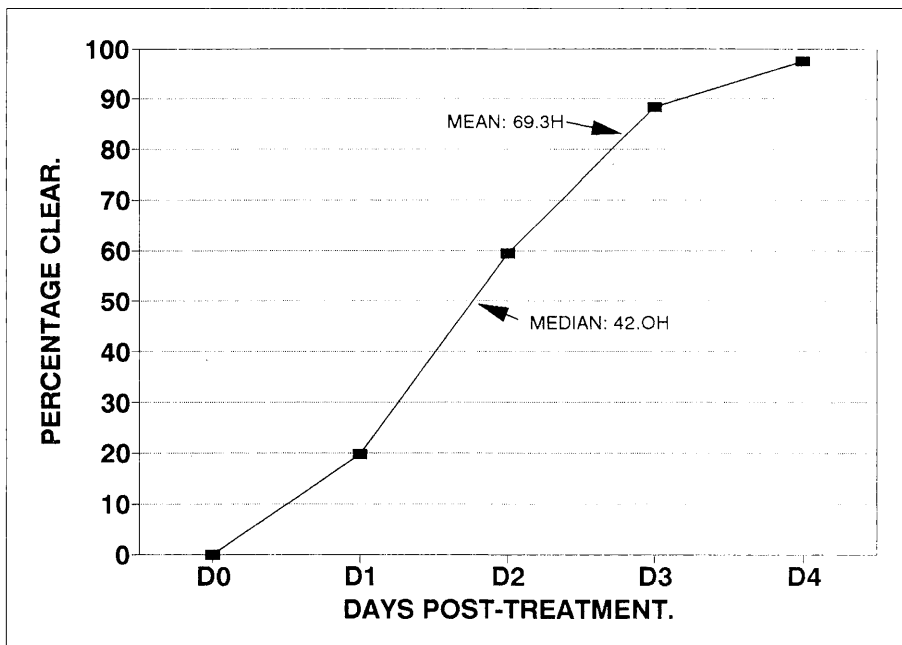


Figure 1:
Proportion of children clear of parasitaemia after treatment.

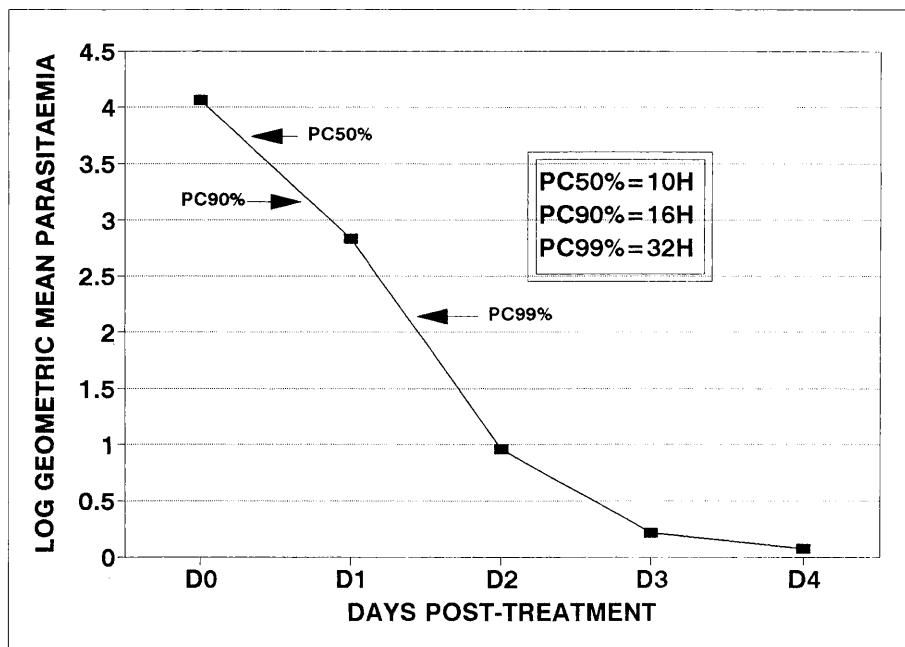


Figure 2:
Clearance of parasitaemia after treatment: mean parasite counts.

Discussion

The extensive studies worldwide with halofantrine have enabled specific analyses of subsets of the data to address questions that could not normally be answered within single studies. The core design of the protocols have meant that data have been collected in a standard format and permit analysis across study. It has therefore been possible to evaluate both efficacy and safety of halofantrine treatment in an important group of patients, infants and very young children.

For the present study an age rather than weight based cut off was chosen, because, for the most part accurate weighing is not available for children in endemic areas. As a result a few children weighing more than 10 kg (30/148 : 20.3%) were included but only two weighed over 12 kg. The range 10 - 12 kg is the lowest dose level for halofantrine included in current prescribing information.

The analysis shows that the efficacy of halofantrine treatment of very small children is comparable to that seen in the general adult and paediatric populations (4, 5) treated in clinical trials. For practical reasons only a small proportion of the children included in this analysis were followed for a full 28 days. The majority (24/36) of these came from a single study conducted in Kenya.

In this longer follow-up it is disappointing to observe that 4 of 31 children recrudesced during the final week of follow-up. However, it has been noted by COULAUD et al. (2) that halofantrine may fail more frequently in non immune patients. Since these very young children have little or no immunity a similar effect may be operating here. In the non immune adult, the tendency to late recrudescence has been overcome by the use of a second treatment 7 days after the first 3 dose course (1, 11) and might be considered as a recommendation for very young children. It is also possible that since these children were studied in holoendemic areas that reinfection could have occurred. However, in endemic areas

Table 1:

Symptoms present pre treatment in 148 children under 2 years of age, and the pattern of clearance post treatment.

| Symptom | Pre N (%) | Clearance (days) | | | | | | |
|----------------|------------|------------------|---------|--------|--------|--------|-------|--------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Fever | 121 (81.7) | 77 (a) 63.6 (b) | 25 84.3 | 9 91.7 | 5 95.8 | 1 96.6 | — | 1 97.5 |
| Pallor | 36 (24.3) | 7 19.4 | 6 36.1 | 2 41.6 | — | 1 44.4 | — | — |
| Vomiting | 27 (18.2) | 19 70.3 | 7 96.3 | 1 100 | — | — | — | — |
| Diarrhoea | 21 (14.2) | 9 42.9 | 6 71.4 | 2 80.9 | — | 2 90.5 | 2 100 | — |
| Rigors | 19 (12.8) | 15 78.9 | 2 89.5 | — | — | 1 94.7 | — | 1 100 |
| Coughing | 14 (9.5) | 5 35.7 | 2 50.0 | — | — | 1 57.1 | — | 1 64.3 |
| Headache | 10 (6.7) | 9 90.0 | 1 100 | — | — | — | — | — |
| Itch | 8 (5.4) | 4 50.0 | — | 1 70.0 | — | — | — | — |
| Nausea | 7 (4.7) | 5 71.4 | 2 100 | — | — | — | — | — |
| Abdominal Pain | 6 (4.1) | 5 83.3 | 1 100 | — | — | — | — | — |

Also recorded; anorexia, weakness, convulsions, jaundice, nervousness, altered consciousness.

(a) Number clear of symptoms

(b) Cumulative % clearance of symptoms

Table 2:

New symptoms occurring 0 - 7 days post treatment in children under 2 years.

| Symptom | N | % |
|----------------|----|-----|
| Cough | 14 | 9.4 |
| Diarrhoea | 10 | 6.7 |
| Vomiting | 7 | 4.7 |
| Fever | 6 | 4.0 |
| Itch | 5 | 3.4 |
| Pallor | 3 | 2.2 |
| Stomatitis | 2 | 1.3 |
| Rash | 1 | 0.6 |
| Abdominal Pain | 1 | 0.6 |
| Anorexia | 1 | 0.6 |

compliance with a week between treatment courses might be difficult to obtain and therefore a shorter gap, such one of 3 days currently under investigation in Thailand, could be used.

It is of interest to note that similar rapid clearance rates are reported with halofantrine in non immune adults (3). The rapidity of clearance may result from a low level of resistance compared to chloroquine. Recent data, however, suggest that halofantrine acts *in vivo* on both trophozoites and schizonts in contrast to quinine and sulphadoxine/pyrimethamine, and this may contribute to rapid parasite clearance (10).

Apart from fever, which was recorded as a symptom in 81.7% of children, pre treatment symptoms were less common than in the adult and overall paediatric populations (4, 5), despite the presence of relatively high parasitaemias in most children. This is consistent with the accepted picture of acute malaria in infants who are usually less symptomatic. Clearance of most initial symptoms and signs was rapid, and had disappeared by day 2 or 3 post treatment. Pallor, the second most common symptom was still present in over 50% of children who had this sign at the end of 1 week. Cough was also very slow to clear in a significant proportion. It is suggested that these were related in some children with other underlying pathology, eg. chronic anaemia or upper respiratory infection, rather than malaria.

Electrocardiograms were not performed in any of the children covered by this analysis, but there was no evi-

dence in retrospect that would suggest the presence of clinically significant QT prolongation or cardiac adverse effects in this group. To date (Sept. 1994) there have been no reports of serious cardiac effects in very young children treated with halofantrine (data on file Smith-Kline Beecham).

Newly emerging symptoms were relatively uncommon. The pattern of these differed markedly from those previously described in adults, with cough, diarrhoea and vomiting predominating. This may result from the children being generally unable to report more subjective symptoms such as headache or dizziness rather than a true difference in emergent symptom rates. The commonest symptom recorded was cough; symptomatology may be due to circulating upper respiratory infections in the study population.

On the basis of this data analysis, halofantrine appears to be an effective and well tolerated treatment for infants and very young children with mild to moderate uncomplicated malaria. Parasite clearance is found to be fast, with symptom clearance essentially mirroring parasite clearance. Side effects attributable to treatment are uncommon, mild and self limiting. For this population halofantrine is a useful addition to the available armamentarium for the treatment of paediatric malaria.

Summary

Malaria in very young children is a major therapeutic challenge in endemic areas where initial infection can occur in the first few months of life. Such children, with limited immunity, are most at risk of severe disease and death. To establish the efficacy and safety of halofantrine in

very young children, a cohort of subjects under the age of 2 years contained in the SmithKline Beecham worldwide clinical trial data base was examined. 148 children, mean age 13.7 months (range 4 – 23 months) with a mean weight of 8.6 kg were identified as having received a standard regimen of 8 mg/kg \times 3 doses. 78.6% had previous malaria attacks. Mean parasite clearance by 7 days occurred in 99.3% of evaluable children, a single case being still parasitaemic at day 7. Parasite clearance time was 69.3 hours and mean fever clearance time 46.8 hours. Recrudescence of parasitaemia occurred in 3.2% of children followed to day 14. The pretreatment symptoms cleared rapidly, usually within 48 hours. Post treatment events included cough in 9.4%, diarrhoea in 6.7% and vomiting in 4.7%.

In general halofantrine was well tolerated and appears a useful and effective treatment for very young children.

Key words Halofantrine, *Plasmodium falciparum*, malaria, treatment, infants.

Zusammenfassung *Halofantrin-Therapie der akuten Malaria tropica bei Säuglingen und Kleinkindern*

Malaria bei sehr jungen Kindern ist eine große therapeutische Herausforderung in Endemiegebieten, wo eine Initial-Infektion in den ersten Lebensmonaten erfolgen kann. Diese Kinder mit begrenzter Immunität haben das größte Risiko für einen schweren, oft tödlichen, Krankheitsverlauf. Um die Wirksamkeit und Sicherheit von Halofantrin bei Kleinkindern ermitteln, wurde eine Gruppe von Kindern unter 2 Jahren, die in der weltweiten Datenbank von SmithKline Beecham erfaßt sind, untersucht. 148 Kinder mit einem Durchschnittsalter von 13,7 Monaten (zwischen 4 und 23 Monaten) und mit einem Durchschnittsgewicht von 8,6 kg, die eine Standardtherapie mit einer Dosierung von 3 \times 8 mg/kg Körpergewicht erhielten, wurden ausgewählt. 78,6% von ihnen hatten bereits früher Malariaanfälle. Bei 99,3% der auswertbaren Kinder erfolgte die Parasiten-Clearance innerhalb von sieben Tagen; in einem einzigen Fall wurden am Tag 7 noch Parasiten nachgewiesen. Die Parasiten-Clearance betrug 69,3 Stunden, die Fieber-Clearance 46,8 Stunden. Eine Rekrudescenz trat nach dem Tag 14 bei 3,2% der Kinder auf. Die Symptome, die sich vor der Behandlung manifestiert hatten, verschwanden schnell, normalerweise innerhalb von 48 Stunden. Nach der Behandlung traten Husten bei 9,4%, Diarrhoe bei 6,7% und Erbrechen bei 4,7% der Kinder auf.

Im allgemeinen wurde Halofantrin gut vertragen und zeigte sich als nutzbringende und effektive Therapie Kleinkindern.

Schlüsselwörter Halofantrin, *Plasmodium falciparum*, Malaria, Therapie, Kleinkinder.

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References

1. BERNARD, J. et al. (1990): Treatment of imported *Plasmodium falciparum* by halofantrine. 59 cases treated. *Médecine Tropicale* 50, 167-171.
2. COULAUD, J. P. et al. (1986): Treatment of imported cases of *falciparum* malaria in France with halofantrine. *Trans. Roy. Soc. Trop. Med. Hyg.* 80, 816-817.

3. DOORDUIJN, J. K., WISMANS, P. J., STUVIER, P. C. (1992):
A prospective study of halofantrine in the treatment of falciparum malaria in non immune subjects.
Proceedings 8th International Congress of Tropical Medicine and Malaria, Jomtien, Thailand 2, 56, Mo P13
(Abstract).
4. HORTON, R. J., PARR, S. N., BOKOR, L. C. (1990):
Clinical experience with halofantrine in the treatment of malaria.
Drugs Exptl. Clin. Res. 16, 497-504.
5. HORTON, R. J., PARR, S. N., BOKOR, L. C. (1992):
The treatment of falciparum malaria in children with halofantrine hydrochloride.
Memorias Instituto Oswaldo Cruz, 87 (suppl. 3), 265-269.
6. KHAN, M. A., NAYYER-REHMAN, G., QAZI, S. A. (1991):
Halofantrine hydrochloride – efficacy and safety in children with acute malaria.
J. Pak. Med. Assoc. 41, 8-10.
7. MASHAKO, M. N. L., KINGWAY, M. P., KAYEMBE, N. (1990):
Treatment of falciparum malaria with halofantrine hydrochloride in a drug resistant region. Analysis of 54
paediatric cases.
Ann. Soc. Belgue. Méd. Trop. 70, 25-32.
8. NOSTEN, F., TER KUILE, F. O., LUXEMBURGER, C., WOOCHOW, C., KYLE, D. E., CHONGSUPHAJASIDDHI, T.,
WHITE, N. J. (1993):
Cardiac effects of antimalarial treatment with halofantrine.
Lancet 341, 1054-1056.
9. WATKINS, W. M. et al. (1989):
The efficacy of halofantrine treatment in chloroquine resistant Plasmodium falciparum malaria in children in
Kenya.
Afrique Médicale 28, 355-359.
10. WATKINS, W. M., WOODROW, C., MARSH, K. (1993):
Falciparum malaria: differential effects of antimalarial drugs on ex vivo parasite viability during the critical
early phase of treatment.
Am. J. Trop. Med. Hyg. 49, 106-112.
11. WEINKE, T. et al. (1992):
The efficacy of halofantrine in the treatment of acute malaria in non immune travellers.
Am. J. Trop. Med. Hyg. 47, 1-5.

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