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Short Report

Comparative effectiveness of artemisinin suppositories and oral quinine in children with acute falciparum malaria

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Resistance to available antimalarial drugs is becoming more widespread (WHO, 1987; BJÖRKMAN & PHILLIPS-HOWARD, 1990), leading to a delayed initial fall in parasite count and a prolonged time to complete clearance. Although it is sequestration of parasites and release of cytokines (WARRELL *et al.*, 1990) that are involved in the symptoms and signs and complications of falciparum malaria, it is generally agreed that a rapid decrease in initial parasitaemia is desirable and may help to prevent the development of complications. Artemisinin and its derivatives, including the suppository form (ARNOLD *et al.*, 1990), quickly reduce parasitaemia (DING, 1988). Since, in terms of numbers affected, most severe morbidity and mortality is in children in rural areas, an effective, convenient and safe preparation used early in the disease could save lives. This study with artemisinin suppositories in children concentrated on the early clearance of parasitaemia, since recrudescence is well recognized with artemisinin in courses lasting under 7 d.

In the same hospital, and with similar criteria for patient inclusion and study methods as previously described (ARNOLD *et al.*, 1990), and with informed parental consent, children between the ages of 1 and 15 years were randomly assigned to receive artemisinin suppositories (kindly provided by Professor Li Guo-Qiao) or oral quinine. The artemisinin dosage schedule was adjusted for age and given for 3 d (Table 1), while the quinine was given as the sulphate orally at 10 mg/kg body weight every 8 h for 10 d. Parasite counts and axillary temperature were measured 6 hourly and the rate of parasite clearance determined for each patient by taking the immediate pre-treatment count as 100% and plotting subsequent 6 hourly counts as percentages of this.

Comparative patient data and the results of treatment in 60 children are shown in Table 2. Defervescence time was 54 h with both drugs, but 50% and 95% parasite clearance was significantly faster in the group receiving artemisinin (6·2 vs 10·9 h and 15·7 vs 32·8 h respectively). Time to complete clearance was also significantly different (25·8 vs 43·0 h for artemisinin and quinine respectively). Among the 30 children receiving oral quinine there was one RII response (reduced but not complete clearance by day 7), 4 delayed RI responses (recrudesced after day 7 but before day 14), 23 S or delayed RI responses (no recrudescence by day 14 but lost to follow-up on day 28), and 2 definite S responses (radical cure, no recrudescence by day 28). Among the 30 children receiving artemisinin suppositories there were 7 delayed RI responses, 21 S or delayed RI responses, and 2 definite S responses.

Side-effects with quinine were those usually reported—nausea and dizziness in a few of the children able to describe symptoms. There were no symptomatic side-effects from the artemisinin suppositories or local effects such as anal irritation.

Table 1. Dosage schedule for artemisinin suppositories (mg)

Age (years)	Day 1 0 h	Day 1 4 h	Day 2[a] AM	Day 2[a] PM	Day 3[a] AM	Day 3[a] PM	Total dose
11–15	600	400	300	300	300	300	2200
7–10	300	300	200	200	200	200	1400
3–6	200	200	200	100	200	100	1000
1–2	100	100	100	100	100	100	600

[a]Suppositories given at 8 hour interval.

Table 2. Patient data and results

	Quinine	Artemisinin
Male/female numbers	16/14	18/12
Age in years[a]	8·6± 4·0	8·1± 4·1
Temperature on admission (°C)[a]	38·6± 0·9	38·8± 0·9
Parasitaemia/μl		
Range	1040–1037000	1008–780000
Mean (arithmetic)[b]	80287±37597	104853±30766[c]
Mean (geometric)	15310	28929
Defervescence time (h)	54·2±29·0	54·2±42·1
Parasite clearance time (h)		
50%	10·9± 8·2	6·2± 3·2[d]
95%	32·8±19·1	15·7± 4·8[d]
Complete	43·0±22·0	25·8± 78·9[d]

[a]Mean±standard deviation.
[b]±Standard error of the mean.
[c]Difference between treatment groups not significant ($P>0·05$).
[d]Significant difference between artemisinin and quinine groups ($P<0·05$).

If the initial dose of artemisinin used in this study is calculated according to body weight, rather than age, 10 children receiving 10–14 mg/kg took 18·9±4·7 h to achieve 95% clearance of parasitaemia, while 20 children receiving over 15 mg/kg achieved 95% clearance in 14·2±3·3 h, a significant difference ($P<0·05$). The minimum dosage should therefore be above 15 mg/kg but it is probably not necessary to go higher than 25 mg/kg.

These results show that artemisinin suppositories rapidly cleared asexual *Plasmodium falciparum* parasitaemia in children and confirm the known problem of recrudescence with this drug. Quinine is also effective but, with one RII and 4 delayed RI responses, there was some resistance present, as reported elsewhere (BJÖRKMAN & PHILLIPS-HOWARD, 1990). In adults, tetracycline is given to potentiate the action of quinine but since tetracycline is

contra-indicated in children under 8–10 years old, monotherapy with quinine may require a higher dosage, with the potential for increased side-effects, or a longer duration of treatment, with the problem of compliance. Alternatively, another drug could be used, such as mefloquine given as a single dose, or treatment could be started with a single dose of artemisinin to bring the parasite count down rapidly followed by a drug such as Fansimef or mefloquine to kill any remaining parasites and prevent recrudescence. Dose and dosage scheduling of artemisinin and its derivatives have been arbitrary or based on pharmacodynamic results and there is an urgent need for pharmacokinetic data and dose-finding studies. However, their absence should not delay considering a study of artemisinin suppositories in the community to see if morbidity and mortality can be reduced, but dosing by body weight rather than age should be used. The lack of side-effects and the safety of artemisinin suppositories, compared with quinine, are additional factors supporting such a study since the suppositories could be kept in the home and given early in the disease, as previously suggested (ARNOLD *et al.*, 1990); that is, they could be used as presumptive treatment to prevent a high parasitaemia developing. In a highly endemic area the risk of treating a fever that is not malaria using a non-toxic drug is outweighed by the potential benefit. The patient is then taken to a health station where a more definitive diagnosis can be made and further appropriate treatment administered.

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