RESEARCH NOTE

LIFE-SAVING RECTAL ARTESUNATE FOR COMPLICATED MALARIA IN CHILDREN

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Abstract. We report the effectiveness of two regimens of rectal artesunate formulation in treating 13 Thai children with cerebral/complicated falciparum malaria. The drug was given at an initial dose of 40 mg/kg bodyweight, in 3 or 4 divided doses in the first 24 hours, followed by 10 mg/kg bodyweight once daily for three consecutive days. Mefloquine, at a dose of 15 mg/kg bodyweight was given orally at 72 hours after the initial dose of artesunate, followed by 10 mg/kg bodyweight 6 hours later. Three cases with cerebral malaria gained consciousness within 20 hours of artesunate administration. The median time required for reduction of parasitemia by 90% of the initial value (P_{90}) in 13 children was 11.2 hours. No recrudescence was observed in any of the patients during the 28-day follow-up period. Plasma concentrations of artesunate and dihydroartemisinin (active plasma metabolite of artesunate) measured in two patients who received the high initial dose regimen (20 mg/kg bodyweight) suggested rapid absorption and adequate plasma concentrations of both compounds following the administration of artesunate *via* the rectal route. Further studies for the optimized regimen of rectal artesunate in the treatment of cerebral/complicated childhood falciparum malaria in areas of multidrug resistance are warranted.

INTRODUCTION

In areas of multidrug resistance, the World Health Organization has recommended rectal artesunate in the treatment of severe or complicated falciparum malaria at the community healthcare level, prior to transferring patients to hospital (WHO, 2000). Rectal artesunate given at a dose of 15 mg/kg bodyweight once daily for 3 days, followed by a single or two-divided doses of mefloquine, has proved effective in treating uncomplicated childhood malaria in Thailand (Sabchareon *et al*, 1998). Artemisinin suppositories at a dose of 80 mg/kg bodyweight given in three divided doses in the first 24 hours, followed by 20 mg/kg bodyweight at 48 and 72 hours was reported effective in treating multidrug-resistant severe malaria in Viet Nam (Cao *et al*, 1997). Looareesuwan *et al* (1997) reported the effective treatment course of rectal artesunate given at a more frequent dosing regimen in adult Thai patients with multidrug-resistant severe falciparum malaria. The drug was given at an initial dose of 20 mg/kg bodyweight in five divided doses in 24 hours, followed by 3 doses of 4 mg/kg bodyweight every 12 hours (total dose 1,600 mg). The mean (SD) value of the time required for 90% reduction of parasitemia (from baseline) was 17.7 (4.5) hours. We report here the effectiveness of intra-rectal artesunate at a dose of 40 mg/kg bodyweight in 3 or 4 divided doses in the first 24 hours, followed by 10 mg/kg bodyweight OD x 3 in Thai

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children with cerebral/complicated falciparum malaria.

METERIALS AND METHODS

From June to August 1999 and March to June 2000, a total of thirteen children with *P. falciparum* malaria were randomly recruited into the study; 6 cases were admitted to Thong Pha Phum Hospital (Kanchanaburi Province), 3 cases to Paholpolpayuhasena Hospital (Kanchanaburi Province), 1 to Mae Sot Hospital (Tak Province), and 3 to the Hospital for Tropical Diseases (Bangkok). All were residents of multidrug-resistant falciparum areas along the Thai-Myanmar border. Written informed consent for participation in the study was obtained from the parents of all children. The study was approved by the Ethics Committee of the Ministry of Public Health, Thailand.

The diagnosis of severe/complicated malaria was based on the categorized clinical and laboratory criteria (WHO, 2000) shown in Table 1. Blood lactate dehydrogenase levels determined in 7 patients were greater than 1,000 U/l, while in one case it was 551 U/l. Thin and thick blood smears were performed in all cases before and at 6 and 12 hours after the start of the first dose of rectal artesunate, then at 12-hours intervals until malaria-parasite negative for two consecutive examinations, and then on days 7, 14, and 28 of treatment. All but one had no previous history of antimalarial treatment within one month, nor urine positive for aminoquinoline or sulfonamide.

Patients were treated with intra-rectal artesunate (Rectocap®: 50 mg and 200 mg/capsule; Mepha, Aesch-Basel, Switzerland) and oral mefloquine (Mephaquin®: 250 mg/tablet; Mepha, Aesch-Basel, Switzerland). Artesunate was given with the aim to rapidly reduce parasitemia, while mefloquine was to totally eradicate parasitemia. Five patients, including one case with cerebral malaria, received an initial 20 mg/kg bodyweight dose of intra-rectal artesunate, followed by 10 mg/kg bodyweight at 12 and 24 hours later, and

Table 1
Baseline characteristics and clinical outcomes of the 13 patients with cerebral/complicated falciparum malaria following the two initial dose levels of rectal artesunate (10 and 20 mg/kg bodyweight).

	Initial dosage of artesunate	
	20 mg/kg (n = 5)	10 mg/kg (n = 8)
Baseline characteristics		
Impaired consciousness	1[a]	2[b]
Jaundice with total bilirubin >3 mg/dl	1	4
>5% asexual *P. falciparum* in peripheral blood	3	5
LDH[c] >1,000 U/l	5	3
Macroscopic hemoglobinuria	1	-
Median parasite count/ml	55,050(5,720-441,440)	204,280(16,500-377,740)
Results		
Median reduction time by 50% of initial parasitemia (P_{50}, hr)	7(3.4-18.2)	6(3.5-14.1)
Median reduction time by 90% of initial parasitemia (P_{90}, hr)	12(6.2-23.1)	11(7.4-22.4)
Median parasite clearance time (PCT, hr)	48(12-60)	24(12-48)
Median fever clearance time (FCT, hr)	44(32-72)	62(20-96)
No. cured at 28 days (%)	5(100)	8(100)

( ), range; [a]Blantyre coma score = 2; [b]Blantyre coma score = 3; [c]LDH: lactate dehydrogenase, data available for 8 cases only (including one case of 551 U/l).

Table 2
Pharmacokinetic parameters of artesunate and dihydroartemisinin derived from 1-compartment open model (with first-order input and output) analysis in two children with hyperparasitemia.

	C_{max} (ng/ml)	t_{max} (hr)	Absorption Lag time (hr)	$t_{1/2a}$ (hr)	$t_{1/2}$ (hr)	V_c/F (l/kg)
Artesunate						
Patient A	800	0.2	0.01	0.7	0.7	21.78
Patient B	988	1.2	0.37	0.05	1	12.22
Dihydroartemisinin						
Patient A	1,220	1	0.16	0.03	0.7	5.83
Patient B	990	1.3	1	0.37	2	18.27

C_{max}: maximum plasma concentration; t_{max}: time to C_{max}; V_c/F: volume distribution of the central compartment; $t_{1/2a}$: absorption half-life (for dihydroartemisinin = half-life of appearance); $t_{1/2}$: elimination half life

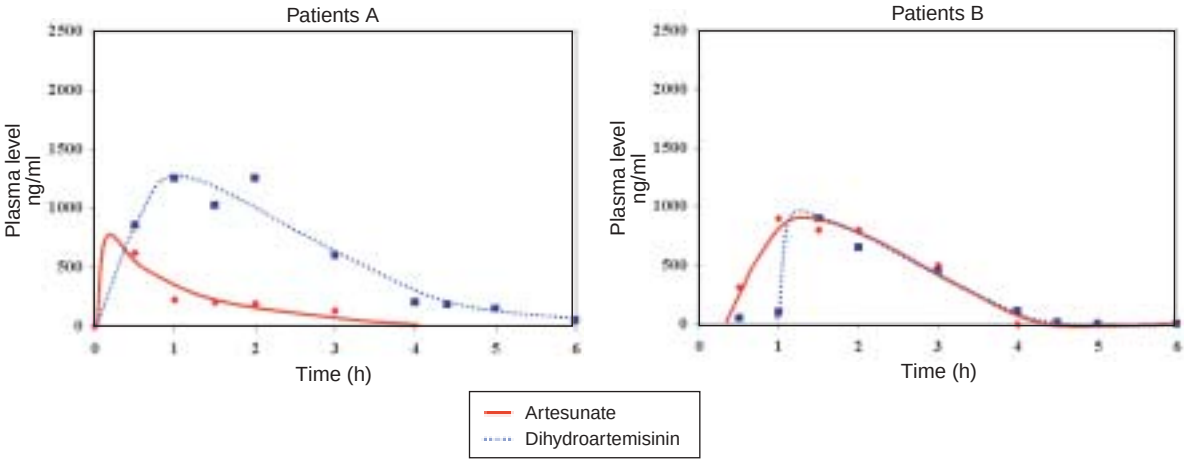

Fig 1–Plasma concentration-time profiles of artesunate and dihydroartemisinin in two children who received an initial 20 mg/kg bodyweight dose of rectal artesunate.

then 10 mg/kg bodyweight once daily for three days. Mefloquine, at a dose of 15 mg/kg bodyweight, was given orally at 72 hours after the initial dose of artesunate, followed by 10 mg/kg bodyweight at 6 hours later. The other eight cases, including two cases with cerebral malaria, received intra-rectal artesunate at 10 mg/kg bodyweight given at 0, 4, 12, and 24 hours of treatment, followed by 10 mg/kg bodyweight given once daily for an additional 3 days. Mefloquine was administered in the same dosage and schedule as the former group.

Serial clinical observations and complete blood counts were assessed to evaluate the efficacy and tolerability of both treatment regimens. No adverse effect was observed in any patient during the treatment. The clinical response showed that intra-rectal artesunate was effective, well-tolerated and can be a life-saving drug in cerebral/complicated multidrug-resistant falciparum malaria in children. All patients recovered from the signs and symptoms of severe malaria with a 100% cure rate (Table 1). In the group receiving a high initial dose of rectal artesunate (20 mg/kg bodyweight), the median (range) fever clearance time (FCT) was 44 (32-72) hours. Median (range) values of the time required for the reduction of parasitemia by 50, 90, and 100% of the initial values (P_{50}, P_{90}, PCT) were 7 (3.4-18.2), 12 (6.2-23.1), and 48 (12-60)

hours, respectively (Table 1). No abnormality in electrocardiogram (EKG) was observed in a child with marked hyperparasitemia (441,440 parasites/μl) before medication, as well as at 4, 12 hours and on day 7 of treatment. A child with cerebral malaria gained consciousness 12 hours after rectal artesunate administration; *P. falciparum* was not detected at 24 hours and defervescence occurred at 32 hours after treatment. In the group receiving a low initial dose of rectal artesunate (10 mg/kg bodyweight), median (range) fever clearance time (FCT) was 62 (20-96) hours. Median (range) values of the time required for the reduction of parasitemia by 50, 90, and 100% of the initial values (P_{50}, P_{90}, PCT) were 6 (3.5-14.1), 11 (7.4-22.4), and 24 (12-48) hours, respectively (Table 1). The two cases with cerebral malaria gained consciousness after 20 and 13 hours of treatment.

DISCUSSION

It was observed in a previous study in African children with moderate falciparum malaria (Krishna *et al*, 2001) that the median relative bioavailability of dihydroartemisinin (the active plasma metabolite of artesunate) following rectal artesunate was significantly higher in the low-dose group (10 mg/kg bodyweight) than the high-dose group (20 mg/kg bodyweight) (58 *vs* 23%). In the present study, however, plasma samples for pharmacokinetic investigation of artesunate and dihydroartemisinin were accomplished only in two patients with hyperparasitemia who received the high initial dose of rectal artesunate (20 mg/kg bodyweight). Blood samples were collected prior to, and at 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 6, 8, 12, and 24 hours of the first dose of rectal artesunate. Concentrations of artesunate and dihydroartemisinin were quantified using high performance liquid chromatography with electrochemical detection at the Faculty of Allied Health Sciences, Thammasat University, Pathum Thani, Thailand (Na-Bangchang *et al*, 1998). Pharmacokinetic profiles obtained from both patients were generally in agreement with those reported previously following the administration of rectal artesunate (Halpaap *et al*, 1998; Sabcharoen *et al*, 1998; Krishna *et al*, 2001), signifying the rapid absorption and biotransformation of artesunate to dihydroartemisinin. Plasma concentrations of artesunate and dihydroartemisin of 800-988 and 990-1,220 ng/ml were reached at 0.2-1.2 and 1.0-1.3 hours, respectively (Fig 1 and Table 2). It was noted that the absorption of artesunate from the rectal formulation was rapid, but may be erratic, especially with the high dose, as evidenced from the result of this study, and that reported by Krishna *et al* (1998). Although the number of patients included was too small to gain a full appreciation of the absorption and disposition kinetics of artesunate and dihydroartemisinin following intra-rectal dose administration in severe childhood malaria, the current data showed that the absorption of artesunate from the rectal formulation was rapid. The rate of absorption was comparable with that observed following oral artesunate, and was sufficiently rapid to allow adequate plasma levels above the minimum inhibitory concentration (MIC) within a few minutes after administration. This would thus be useful for treating falciparum malaria with moderate level severity. Further studies of artesunate suppositories in the treatment of cerebral/complicated falciparum malaria in children in multidrug resistance areas are warranted, to ensure the safety and the optimum intervals and dosages of such a regimen.

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