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Pharmacokinetics/Pharmacodynamics findings after repeated Administration of ARTESUNATE thermostable suppositories (RECTOCAPS)* in Vietnamese patients with uncomplicated malaria

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SUMMARY

In recent years, Artemisinin and particularly one of its derivatives – Artesunate (ART – has become an essential alternative for treatment of both uncomplicated and severe falciparum malaria in Asia and Africa as well.
Therefore, these compounds are still and inccreasingly in the focus of interest because of quick acting of this drug, is able to help even unconscious to overcome the malaria attack, when administered by injection. As an alternative, RECTOCAPS have been developed and their use is meanwhile well established. From earlier studies in children, suffering from plasmodium falciparum malaria, we obtained a high level of DHART in the blood, but as expected also a rapid decline in the levels of both DHART and ART. A second administration of ART was additionally applied 4 hours after the first administration. DHART and ART plasma levels were found to last longer on an assumed therapeutic level than those obtained after one administration only. The fever clearance and the parasitemia reduction rates were found to be effective according to this dosing regimen. In view of these findings, we decided to conduct the actual described study by administering 200 mg of ART every 3 hours (0, 3, 6 and 9 h) by the rectal route.
Soft geiatine capsules (RECTOCAPS) containing 200 mg of ART GMP - type each (Artesunic acid) were administered by rectal route. Each patient received four RECTOCAPS capsules (4 x 200 mg of ART) over a 3 h period.
12 adult patients with uncomplicated malaria were selected. Age, weight, height, body temperature, parasite counts before treatment and their evolution until 96 h are determined. Blood samples were taken at short time intervals after starting with the first medication: 0, 30 min, 60 min, 3 h, 6 h, 9 h, 12 h, 24 h, 36 h, 48 h, 60 h, 72 h, 84 h, 96 h and 108 h. The aliquots of all the blood samples were used for performing parasite counts. Plasma obtained following the traditional procedure was kept at -40°C until analysis. HPLC technique with electrochemical detector was used for quantification of ART and DHART. From the blood

* RECTOCAPS Plasmotrim ® MEPHA Ltd, Switzerland

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concentration values of ART and DHART, the following observation can be derived: the onset of action is observed within the first half hours, therapeutic levels of the drug obtained (89 μg/ml ART compared to 84 μg/ml DHART). The DHART levels are somewhat higher than those of ART (a peak concentration after 6 h starting medication of 151 μg/ml ART as compared to 276 μg/ml DHART). The variations as a function of frequency of DHART uptake are much less marked than those observed for ART. Another finding is that after the administration, some sort of a plateau of DHART and ART is built up, lasting at least from 9 to 12 hours with DHART level of about 190 μg/ml and ART of 90 μg/ml. In the case of single-dose administration, the levels of both compounds were below the detection threshold after three hours.
With regard to the parasite counts, although there were inter-individual variations, it should be noted that after 48 hours a high proportion of the patients (8 out of 12) was completely clear of parasites. Similar results were observed with regard to the body temperature (7 out of 12 returned to normal temperature 36 hours after starting the therapy). The findings of the study support the RECTOCAPS application principle resulting in effectiveness both for the velocity of drug uptake as well as for the height of plasma levels. Repeated administration of ART can extend the duration of therapeutic plasma levels of the drug.

INTRODUCTION

In recent years, Artemisinin and particularly one of its derivatives - Artesunate - has become an essential alternative for both uncomplicated and severe falciparum malaria in Asia and Africa.

The use of these drugs has become more frequent in other parts of the world as well in spite of the extraordinary therapeutic success of this therapy, its use is not nearly as widespread as it deserves to be. There are a number of reasons for this, the first of which is that the cost of this medication is still relatively high for the populations in developing countries that are in need of it. However there are indications that the price will be substantially reduced in the near future. Another factor that has impeded the adoption of Artesunate is the claim made by some international bodies, that wider use of these drugs would lead to resistance of the parasite. It should be borne in mind, however, that there is sufficient evidence that the Artemisinin family of drugs has a mode of action that is totally different from that of the classical antimalaria drugs to which the resistance phenomenon has been established. Furthermore, since 1985, millions of people in China and Vietnam have been treated with drugs of this family with no cases of resistance reported.

On this point, homage should be paid to our Chinese colleagues for their extraordinary discovery that they saved the lives of millions of malaria patients.

Nevertheless, the high rate of recrudescence reported by several authors (1,2,3,4) remains a problem. The Chinese schema for treatment of uncomplicated malaria by the administration at 0, 4, 24 and 48 hours have resulted in a recrudescence rate from 45 to 60 % (5). However, other studies conducted at the same period of time, have reported a recrudescence rate of only 5 % when the treatment lasted for 5 days (5). These authors suggested that another antimalarial (Mephloquine) be administered after the 3 days of treatment with artemisinin and derivatives to reduce the high rate of recrudescence..

At the time that these results were reported, no reliable pharmacokinetic data were available. It is now known that the pharmacokinetics of artemisinin and derivatives are directly related to the therapeutic effect. In one of our studies in children with plasmodium falciparum malaria, we observed not only a high level of dihydroartemisinin in the blood but also a rapid decline in the levels of dihydroartemisinin and artesunate and that 4 hours after the first administration, the level for both compounds were below the detection levels. A second administration of artesunate was given 4 hours after the first administration.

The dihydroartemisinin and artesunate values, measured 1 hr later were found to be practically the same as those obtained after the first administration, the fever clearance and the parasitemia rates were also found to be surprisly good.

In view of these very encouraging results, we decide to conduct the study reported in this paper, in which 200 mg of artesunate was administered every 3 hours (0, 3, 6 and 9 h) by rectal route (RECTOCAPS suppositories).

EXPERIMENTAL CONDITIONS AND SUBJECTS OF THE STUDY

The protocole of this study has been approuved by the local ethics committee.

12 adult patients with uncomplicated malaria were selected. Age, weight, sex, height and body temperature before start of treatment are shone Table I. Parasite counts before treatment and their evolution until 96 hrs are given in Table II.

Soft gelatine ampoules (RECTOCAPS from MEPHA Company) containing 200 mg of Artesunate (Artesunic acid) were administered by rectal route. Each patient received four RECTOCAPS ampoules (4 x 200 mg of Artesunate) ever a 3 h period. Since the study was designed to establish the pharmacokinetic parameter values of Artesunate under conditions of repeated administration, blood samples were taken at the following time intervals:

Table I: Temperature Chart for the 12 subjects (taken every 12 hours)

N°	101	102	103	104	105	106	107	108	109	110	111	112
Age	37	25	40	50	37	24	36	19	49	52	42	46
Weight	44	38	34	53	44	64	38	51	70	52	48.5	53
Height	165	145	157	165	163	171	145	169	165	153	157	156
	$7^{15}/40°$	$18^{15}/37.6°$	$6^{40}/38°$	$17^{30}/38°$	9/39°	17/38.2°	$15^{35}/39°$	$6^{40}/37°$	$20^{30}/39°$	$7^{30}/37°$	$10^{45}/40.5°$	$18^{40}/38°$
	$19^{15}/38°$	$6^{15}/38°$	$18^{40}/37.2°$	$5^{30}/38.2°$	21/38.2°	5/39.5°	$3^{35}/37°$	$18^{40}/37.2°$	$8^{30}/39°$	$19^{30}/37°$	$22^{45}/38.5°$	$6^{40}/37°$
	$7^{15}/37.2°$	$18^{15}/37.2°$	$6^{40}/38.4°$	$17^{30}/37.5°$	9/38.5°	17/40°	$15^{35}/38.5°$	$6^{40}/36.8°$	$20^{30}/40°$	$7^{30}/38.5°$	$10^{45}/40.5°$	$18^{40}/39°$
	$19^{15}/36.8°$	$6^{15}/36.5°$	$18^{40}/36.5°$	$5^{30}/36.8°$	21/37.2°	5/40°	$3^{35}/36.5°$	$18^{40}/37.2°$	$8^{30}/39.2°$	$19^{30}/37.2°$	$22^{45}/36.5°$	$6^{40}/37.5°$
	$7^{15}/37°$		$6^{40}/37.5°$		9/36.8°	17/37.2°	1535/37.2°	$6^{40}/38.4°$	$20^{30}/36.5°$	$7^{30}/37°$	$10^{45}/37.2°$	$18^{40}/36.8°$
			$18^{40}/39.6°$		21/36.4°	5/36.2°	335/36.5°	$18^{40}/37.5°$	$8^{30}/36.8°$	$19^{30}/37.2°$	$22^{45}/36.8°$	$6^{40}/37°$
			$6^{40}/37.2°$		9/36.8°		1535/36.8°	$6^{40}/38.5°$	$20^{30}/36.5°$	$7^{30}/37°$	$10^{45}/37°$	$18^{40}/36.8°$
			$18^{40}/37.5°$		32/36.8°		335/37°	$18^{40}/37°$	$8^{30}/37.4°$		$22^{45}/37°$	$22^{45}/37°$
			$6^{40}/36.5°$		9/37°			$6^{40}/37°$	$20^{30}/37°$			
			$18^{40}/37.2°$						$8^{30}/37°$			
			$6^{40}/37°$									
	36 h	36 h	48 h	36 h	36 h	48 h	36 h	84 h	48 h	36 h	48 h	48 h

Table II: Parasite Counts

Sex	M	F	F	M	M	M	M	M	M	F	F	F
Age	37	25	40	50	37	24	36	19	49	52	43	46
Weight	44	38	34	53	44	64	38	51	70	52	48.5	53
Height	165	145	157	165	163	171	145	169	165	153	157	156
0	561	155000	37600	4697	643	110714	20000	1925	7778	743	26458	58333
30'	552	119231	35878	4189	620	110714	17241	1845	6774	584	20934	52128
60'	566	103333	30322	3726	627	103353	16854	1540	5250	573	19639	48039
3 h	534	59615	29560	3563	567	10353	13043	1265	2646	496	19050	37692
6 h	506	32667	22927	3183	559	91177	12605	1183	2142	336	17972	28488
9 h	483	16667	18990	2217	544	86111	12000	908	92	177	17009	26630
12 h	423	7831	17296	78	544	73810	11364	660	38	7	19050	2058
24 h	561	465	5978	6	537	67391	7143	110	4	0	17318	98
36 h	423	372	5189	0	38	899	2467	0	0	0	103	0
48 h	184	0	2256	0	0	28	510	0	0	0	11	0
60 h	9	0	1880	0	0	0	135	0	0		0	
72 h	0	0	0	0			30		0		0	
84 h			0				0		0			
96 h			0				0					
108 h							0					
	60 h	48 h	72 h	30 h	48 h	60 h	84 h	48 h	36 h	24 h	60 h	36 h

0,30 min, 60 min, 3 h, 6 h, 9 h, 12 h, 24 h, 36 h, 48 h, 60 h, 72 h, 84 h, 96 h and 108 h.

The aliquots of all the blood samples were used for parasite counts. Plasma obtained after traditional procedure was kept at -40°C until analysis. HPLC technique with electrochemical detector was used for quantification of Artesunate and Dihydroartemisinin. The experimental conditions (colonne, mobil phase, internal standard etc) have been described in detail in one of our previous publications (5).

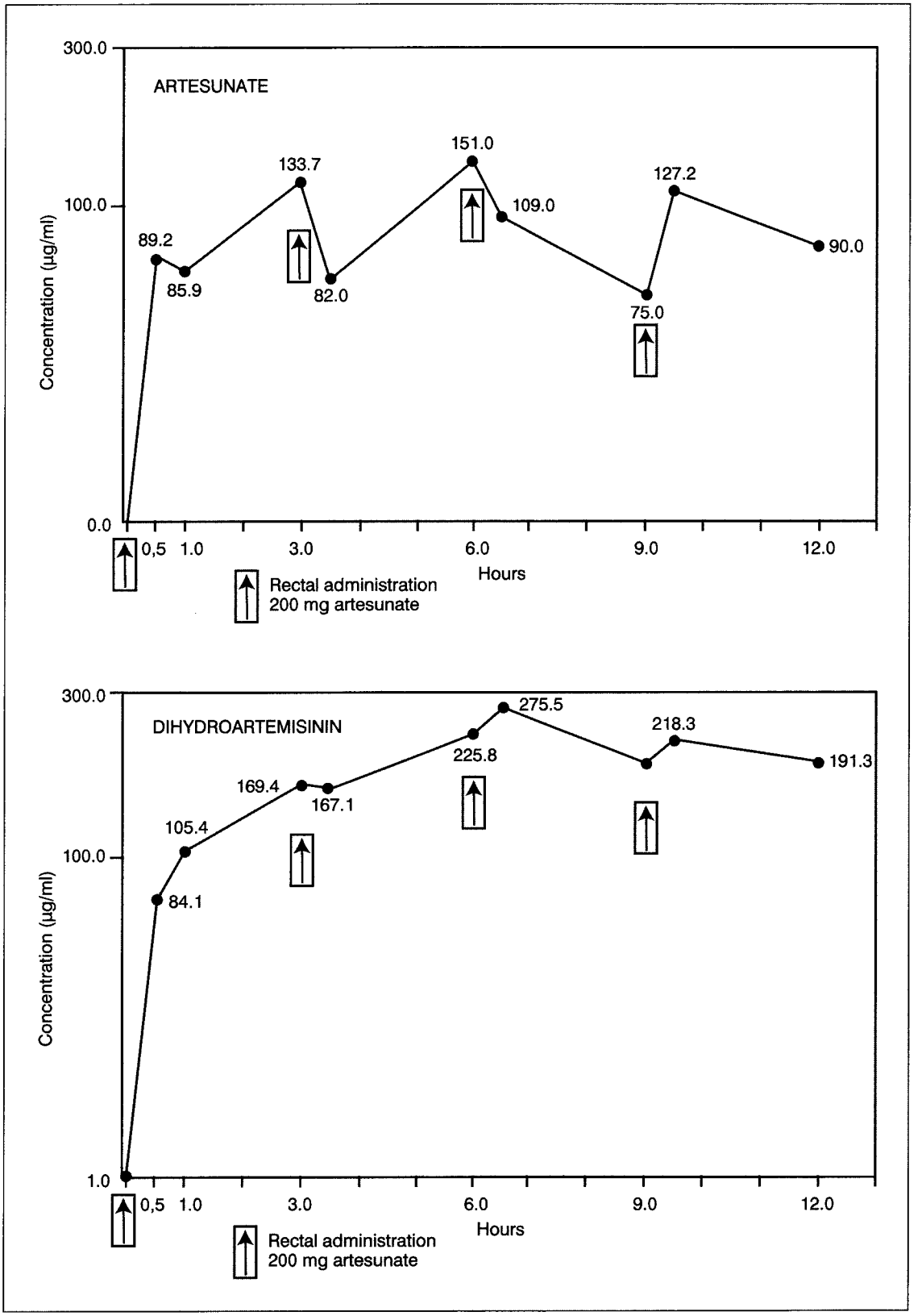
ARTESUNATE
300.0
100.0
0.0
Concentration (µg/ml)
89.2
85.9
133.7
82.0
151.0
109.0
75.0
127.2
90.0
0,5
1.0
3.0
6.0
9.0
12.0
Hours
Rectal administration
200 mg artesunate
DIHYDROARTEMISININ
300.0
100.0
1.0
Concentration (µg/ml)
84.1
105.4
169.4
167.1
225.8
275.5
218.3
191.3
0,5
1.0
3.0
6.0
9.0
12.0
Hours
Rectal administration
200 mg artesunate

Fig 1

RESULTS AND DISCUSSION

The blood level values of artesunate and dihydroartemisinin are shown in Fig. 1. From these results, two important observations can be made. First, that the dihydroartemisinin levels are substantially higher than those of artesunate (about 2 x higher) and also that the variations as a function of frequency are much less marked than those observed for artesunate.

The second note worthy point is that in spite of the relatively limited number of administrations, a plateau of dihydroartemisinin (of about 200 μg/ml) was obtained and this was also true for artesunate although with slightly lower values.

It should also be noted that 12 hours after this first administration of RECTOCAPS the average dihydroartemisinin level was about 200 μg/ml and about 100 μg/ml for artesunate.

These values should be considerer in the light of finding that in the case of a single administration, the levels of both compounds were below the detection threshold after only three hours.

With regard to the parasite counts, although there were inter-individual variations, it should be noted that after 48 hours most of the patients (8 out of 12) were completely clear of parasites and after 60 hours only 2 patients still had parasites. Similar favourable results were observed with regard to temperature (7 out of 12 returned to normal temperature 36 hours after the start of therapy (Table l).

The same experimental protocol has been used in 8 patients with severe malaria. Although the parasite counts and the temperature values are very similar to those found in patients with uncomplicated malaria, it was unfortunately not possible to quantify artesunate and dihydroartemisinin because the analytical technique used was not adequate for blood samples with a high hemolysis rate as is the case in severe malaria patients.

The findings of this study are very encouraging, not only because the clearly show the effectiveness of repeated administration of Artesunate in the form of RECTOCAPS but also and more importantly, because they strongly suggest that it would be of great interest to conduct a further study of which the protocol would be specifically designed to investigate the effect of frequent administration on recurrency.

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