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The Surprising Efficiency of *Artemisia annua* Powder Capsules

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Abstract

The administration of powdered leaves of *Artemisia annua*, used as preventive treatment of malaria attack, was evaluated in 25 patients, most of them children, and all of them were operated for orthopaedic disorder. The duration of the treatment was 36 hours in 11 patients and 60 hours in 14 patients. The average parasitemia was reduced from 432 parasites/ml to 165 parasites/ml, i.e. 62% improvement, without significant difference according to the duration of the treatment. The efficacy was similar whatever the age and the weight of the patient. These results were obtained with a very low amount of powder (400 to 500 mg per day), and with very low quantity of artemisinin (0.4 to 0.5 mg per day). It is concluded that the *Artemisia annua* powder is apparently more effective than the tea preparation, but more costly and maybe not routinely available. The tea preparation, inexpensive and available everywhere, is still the best method for prevention and treatment of malaria on a large scale and should be preferred in the poorest countries.

Keywords: *Artemisia annua;* Pediatric orthopaedics; Plasmodium; Parasitemia

Introduction

During numerous surgical interventions in pediatric orthopaedics conducted with crippled children in Central African Republic, we have frequently been confronted with post-operative high temperatures, occurring the day following or two days after the surgery, which were attributed to malaria and were treated with Quinine salts administration (Quinimax). During a recent session, we investigated the presence of *Plasmodium falciparum* in the blood of some asymptomatic children, with a positive result in all investigated cases.

Artemisia annua administered as tea is known since centuries for its antimalarial effect, due to artemisinin as well as numerous other flavonoids and constituents. Although easy to prepare, and moreover inexpensive, the tea preparation was considered as not perfectly adapted and difficult to use in a surgical context, and we turned towards administration of powdered leaves of *Artemisia annua* in capsules, which were used as preventive treatment of malaria attack during the immediate post-operative period in operated children. The administration of powdered leaves also presents the advantage to deliver the « totum », i.e. the whole set of molecules present in the plant, synergically acting with artemisinin. A Chinese research team [1] had already found in 1992 that gelatine capsules of Artemisia annua extract used in pharmacological and clinical trials on mice gave a cure rate of 100% for *Plasmodium berghei* and *Plasmodium vivax* infections. In recent years other medical teams (Saint-Hillier, Klabes, Tumaini) in Tanzania, Mali, Burundi, DRCongo have been working with *Artemisia annua* capsules on adults and children with excellent results and no side effects. A surprising high level of transfer of artemisinin into the bloodstream from the plant material vs. the pure drug had already been noticed by Weathers et al. [2].

The aim of this study was to evaluate the effectiveness of this preventive treatment. It was conducted during a surgical session in Central African Republic in November 2012.

Materials and Methods

Twenty five patients were included in the study

22 children with an average age of 8 years and 4 months (1-16) and 3 adults with an average age of 27 years (18-40). All patients were operated for an orthopaedic problem (Table 1). Besides the *Plasmodium falciparum* investigations, the preoperative investigation included detection of digestive parasites (positive in all cases) and HIV test (negative in all cases except an adult).

Protocol

The *Artemisia annua* used was the Luxembourg variety, harvested at the site of Walferdange in 2009, dried in industrial equipment at 35°C and covered by the Phytosanitary Certificate No EC/LU/11773.

The *Plasmodium falciparum* blood concentration was investigated twice: once before starting the preventive treatment, and once at J+2, i.e. on the morning of the second post-operative day. The duration of the treatment was as following:

In 14 cases the treatment was started on the day before the surgery (J-1): every patient received 2 capsules per day during 2 and half days (2 capsules on evening at J-1, 2 capsules on evening at J+0, 1 capsule on morning and evening at J+1 and 1 capsule on the morning at J+2). In these cases, the treatment was administered during 60 hours.

In 11 cases, because of purely logistical reasons (the patient was absent the day before the surgery when the capsules were distributed), the treatment started at J+0: these 11 patients received 2 capsules on evening at J+0, 1 capsule on morning and on evening at J+1 and 1 capsule on the morning at J+2. In these cases the treatment was administered during 36 hours.

For the younger patients (less than 3 years of age) the capsules were opened and the powder was administered with milk or mashed manioc. Capsules n°1 was used for patients with weight under 20 kg; all other patients received capsules n°0.

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Results

Biological results

The average parasitemia before starting the treatment was 432 parasites/ml of *Plasmodium falciparum* (160-910) (Table 1). The average parasitemia at the end of the treatment was 165 parasites/ml (0-320), corresponding to an average improvement of 62%; one patient (#18) showed no decline in parasitemia.

For the 11 patients treated during 36 hours, the parasitemia decreased from 395 to 142, i.e. a 64% (23%-100%) improvement. For the 14 patients treated during 60 hours, the parasitemia decreased from 461 to 183, i.e. a 60% (<14%-85%) improvement.

Clinical results

The treatment was perfectly tolerated in all cases. No digestive intolerance was observed. No febrile reaction was observed. The post operative course was considered as uneventful in all cases. The postoperative oedema, frequently observed especially after postero-medial release in congenital club foot was unusually moderate.

Antinociceptive effect

We noticed a substantial post operative antinociceptive effect. The administration of analgesics (Paracetamol) during 12 to 18 hours after surgery could be significantly reduced. This effect has been described in the literature [3] for other artemisia species like *Artemisia vulgaris*. It is does not related to artemisinin.

Antibacterial and anti-inflammatory effects

We did not have the possibility in this study to evaluate the impact of the *Artemisia annua* administered on the bacterial load in the patients. It is well known that this plant has strong sterilizing properties on faecal *Escherichia coli* and *Streptococci* [4]. Extracts of the herb with low artemisinin content activate the lymphocytes (personal communication P. Lutgen) and have also a strong anti-inflammatory effect as demonstrated by reduction of the IL-6 and IL-8 secretion. All this may explain the improved health status after surgery [5].

Discussion

These results are preliminary results only, based on evaluation of a small series, without control group. However the laboratory tests were

	NAME	Age	Diagnosis	Parasitemia before treatment	J-1	J+0	J+1	J+2	Parasitemia after treatment	% improvement
1	Y. M.	7	4ceps retraction	350	2 gel.	2 gel	2 gel.	1 gel.	80	77%
2	M. A.	22	burn (skin graft)	400	2 gel	2 gel.	2 gel.	1 gel.	120	70%
3	B. R.	40	biceps paralysis	400	2 gel	2 gel.	2 gel.	1 gel.	80	80%
4	T. J.	14	club foot	640	2 gel	2 gel.	2 gel.	1 gel.	120	81%
5	G. C.	11	genu varum	240		2 gel.	2 gel.	1 gel.	160	33%
6	Y. A.	13	club foot	440		2 gel.	2 gel.	1 gel.	320	27%
7	M. D.	12	spasticity	300		2 gel.	2 gel.	1 gel.	160	47%
8	Y. Z.	3	club footl	320	2 gel	2 gel.	2 gel.	1 gel.	80	75%
9	M. R.	7	Pott (cyphosis)	160		2 gel.	2 gel.	1 gel.	80	50%
10	M. G.	7	4ceps retraction	910	2 gel	2 gel.	2 gel.	1 gel.	240	74%
11	S A.	18	burn (skin graft)	520	2 gel	2 gel.	2 gel.	1 gel.	80	85%
12	C. T.	5	knee tumor	420		2 gel.	2 gel.	1 gel.	0	100%
13	N. K.	6	genu valgum	580		2 gel.	2 gel.	1 gel.	40	93%
14	Y. G.	15	hand tumor	640		2 gel.	2 gel.	1 gel.	40	94%
15	N. E.	1	club foot	360	2 gel	2 gel.	2 gel.	1 gel.	160	55%
16	D. D	5	club foot	400	2 gel	2 gel.	2 gel.	1 gel.	160	60%
17	R. P.	13	club foot	620	2 gel.	2 gel.	2 gel.	1 gel.	400	35%
18	K. M.	12	stiff hip	420	2 gel.	2 gel.	2 gel.	1 gel.	480	-14%
19	N. J.	2	genu valgum	320		2 gel.	2 gel.	1 gel.	160	50%
20	K. J.	7	genu valgum	520		2 gel.	2 gel.	1 gel.	400	23%
21	W. I.	2	club foot	400	2 gel.	2 gel.	2 gel.	1 gel.	240	40%
22	Y. Z.	2	club footl	400	2 gel.	2 gel.	2 gel.	1 gel.	240	40%
23	B. R.	14	4ceps retraction	320	2 gel.	2 gel.	2 gel.	1 gel.	80	75%
24	P. Z.	11	burn (skin graft)	240		2 gel.	2 gel.	1 gel.	160	33%
25	O. M.	14	chronic osteitis	480		2 gel.	2 gel.	1 gel.	40	92%
	Mean values			432					165	62%
	1 day ½ treatment			395					142	64%
	2 days ½ treatment			461					183	60%
	<5 years			374					149	60%
	>6 <13 years			413					200	52%
	>13 years			496					142	71%

Table 1: The series and the results observed.

performed in the same laboratory, most often by the same technician. Therefore the possible error in the pre and post operative measurements can be considered as similar and negligible, giving credibility to the results, and making possible some provisional conclusions.

All patients presented with a pre-operative asymptomatic parasitemia; this has been already well documented [6]. In our study the aim was not to eradicate the parasites from the blood, but to decrease enough the parasitemia during the first post operative days to avoid any malaria attack, and the treatment was intentionally not extended after the second postoperative day. Nevertheless the efficacy of the *Artemisia annua* powder which was observed in this study is an argument for expecting a lasting effect if used on a long term period for malaria treatment, as it has been demonstrated with tea preparation [7].

Although 3 years old, the *Artemisia annua* powder was very effective against *Plasmodium falciparum*, suggesting that all constituents had stayed stable even after some years. The leaves were kept in a dry place, without special precaution.

In this study, the prevention of malaria with capsules of *Artemisia annua* powder was effective clinically and biologically in almost all cases, allowing a decrease of the parasitemia to the third of the initial value. The decrease was rapidly obtained, as soon as after 36 hours and it was unchanged after 60 hours. An increase of the parasitemia was observed in one case only (patient n°18), without any clinical manifestation. Possibly in this case the treatment allowed cancellation of a beginning malaria attack.

The amount of powder administered was very low: the quantity of powder present in a capsule n°1 was about 200 mg, and the quantity of powder present in a capsule n°0 was about 250 mg. That means that about 400 to 500 mg of *Artemisia annua* powder was given per day. The powder was obtained from the Luxemburg variety, where artemisinin content is about 0,1%, and it may be estimated that about 0.4-0.5 mg of artemisinin was daily administered. This quantity is lower than the recommended quantity when ACT is used and it is also considerably lower than the quantity measured in one litre of tea: 12 mg in the study of Mueller [8], 94 mg in the study of Räth et al. [9], 40-46 mg in the study of Silva et al. [10]. Nevertheless in spite of this very low quantity the treatment with *Artemisia annua* powder was very effective.

Another interesting fact is the same efficacy on the parasitemia whatever the age and thus whatever the weight of the patient: the parasitemia decreased of 60% in children less than 5 years old, of 52% in children 5 to 13 years old, and 71% in patients older than 13 years. This suggests a remarkable efficacy of the powder even at a low dosage. Now increasing the dosage may increase the efficacy and this should be further evaluated. The advantage of the *Artemisia annua* powder compared to the tea preparation is to favour the supply of all the molecules present in the plant, and especially polysaccharides, essential oils [11] and flavonoids. It has been demonstrated that these molecules increase the artemisinin action [12] and that they also have a direct specific antimalarial action [13-15]. Recent studies by the Weathers group using *P. chabaudi* infected rodents showed complete reduction in parasitemia within 30 hrs after oral consumption of a single dose of dry powdered leaves of *A. annua* [16].

The administration of *Artemisia annua* powder is easier and apparently more effective than the tea preparation. However, the capsules are costly and might not be routinely available in remote areas. In our opinion, capsules are not perfectly fitted for use of *Artemisia annua* at a large scale. So promoting a local production of *Artemisia annua* and its administration in tea preparation is still the best method for prevention and treatment of malaria and should be promoted in the poorest countries. Nevertheless another possibility is administration of powder if the plant can be ground with the traditional pestle. The use of capsules as suppositories remains an option in specific conditions, like severe malaria.

Note : During the same surgical session, 5 patients not included in the series (4 adults and one child) presented a malaria attack, occurring in one case despite a prevention using Malarone, in 2 cases without preventive treatment, et in 2 cases persisting despite a standard treatment with ACT during more than 10 days. These 5 patients were treated with capsules at a greater dosage: an initial dose of 3 capsules when starting the treatment, then 4 capsules per day during 7 days. In all 5 cases a rapid relief of the functional troubles and hyperthermia was observed after 24 hours. A dosage of the parasitemia was performed before and during the treatment (after 60 hours) in two cases: in one case (an adult) the *Plasmodium falciparum* concentration decreased from 1500 to 180 parasites/ml. In the second case (a child) the *Plasmodium falciparum* concentration, which had increased from 240 to 8400 parasites/ml in 24 hours before starting the treatment, decreased to 80 parasites/ml after two days and half.

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