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TREATMENT OF DERMAL CYSTICERCOSIS WITH PRAZIQUANTEL (*). A NEW CESTOCIDAL AGENT

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SUMMARY

Twenty adult patients presenting dermal cysticercosis without cerebral or ocular involvement were treated with praziquantel. The first eleven cases received 60 mg/kg/day and the last nine cases 30 mg/kg/day. In both groups the daily dose was split into three oral intakes 4 to 6 hours apart and the drug administration lasted for 6 consecutive days. The latter group of patients also got dexamethasone, 3 mg daily, from one day before until four days after the treatment period with praziquantel. The drug proved to be 100% efficacious as demonstrated histopathologically by the death of the cysticerci of **Taenia solium (Cysticercus cellulosae)** in serial biopsies taken from the 2nd week on after the end of treatment, as well as clinically by the steady disappearence of the dermal nodules during the 6 months following the therapy. Tolerance of praziquantel was good as the incidence and severity of side-effects were not relevant. The drug safety was confirmed through laboratory tests which failed to detect any abnormal findings related to the hematopoietic, liver and kidney functions.

INTRODUCTION

Praziquantel, an heterocyclic isoquinoline derivative, is a new synthetic compound highly active in experimental and human infections caused by cestodes [1,8,12,13,14]. It acts against **Cysticercus bovis**, the larval stage of **Taenia saginata**, in naturally infected calves as well as against **Cysticercus cellulosae**, the larval stage of **Taenia solium**, in naturally infected pigs [2,5,15]. Extensive pharmacological and toxicological studies had demonstrated the tolerance and safety of praziquantel in all tested animal species, including controlled trials involving health volunteers [4,7].

This clinical trial was carried out with the aim of assessing the efficacy of this new cestocidal agent in the treatment of human dermal cysticercosis caused by **Cysticercus cellulosae.**

Trial subjects and Methods

All twenty patients were treated at the Department of Infectious and Parasitic Diseases, Medical School, Federal University of Paraná, Curitiba, Brazil. Thirteen cases were admitted to the Hospital during the treatment period whereas seven cases were treated at the outpatient clinic. Praziquantel was administered per os for six consecutive days. The daily dose was split into three intakes 4 to 6 hours apart. The first 11 patients received 60 mg/kg/day and the last nine patients half that dose. This second group also received 1 mg of dexamethasone t.i.d. starting one day prior to the praziquantel intake. The corticoid administration was maintained until four days after finishing the treatment with praziquantel. The daily dose of dexamethasone was gradually decreas-

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ed during the last three days. The rationale for the concomitant corticotherapy was to minimize the potencial risk of inflammatory reactions in the brain triggered by the release of antigens following the death of the parasite within the C.N.S. if an unsuspected case of neurocysticercosis was inadvertently treated [11].

Thirteen patients were males, seven females. Their ages varied from 23 to 58 years (mean, 33 ± 9). The duration of the disease extended from 6 to 36 months, in average 16 ± 7.5. The number of dermal nodules ranged from 8 to 34 with a median and mode of 10 and a mean of 13.1. These nodules were non-adherent to the subjacent tissue, painless to palpation and had an elastic consistency. They started to appear in successive bouts in different areas to the body, mainly the chest, back, arms and neck. Figure 1 displays a human body sketch of a theoretical patient having the average number of nodules in the most common localizations as found in our trial subjects.

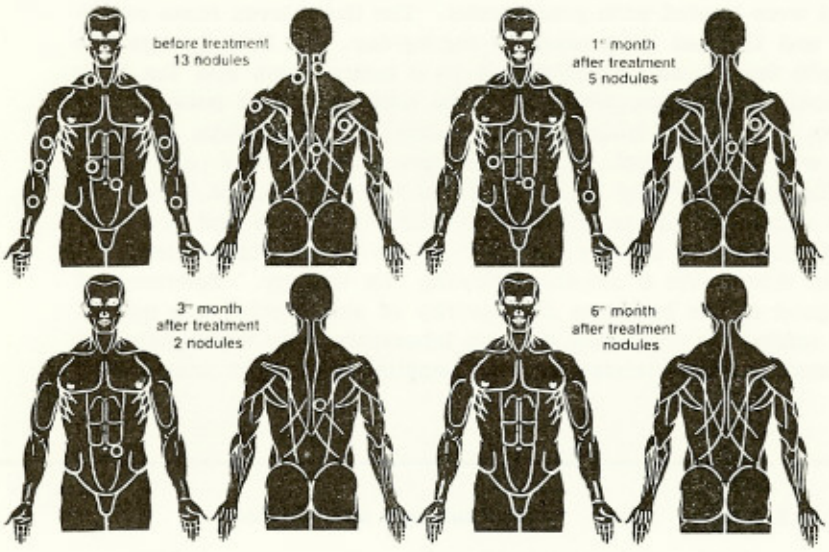


Fig. 1 — Sketch of the human body displaying a theoretical patient having the average number of dermal cysts in the most common localizations as found in our trial subjects, before and on the 1st, 3rd and 6th month after treatment.

To confirm the diagnosis, two cysts were surgically removed from each patient under local anestesia. One cyst was subjected to macroscopic inspection and testing of its vitality. The cysts appear like a spherical or ovoid vesicle having a thin, smooth and lustrous wall. By transparence one could see using a magnifying glass a limpid fluid in its interior with a small yellowish invagination corresponding to the scolex of the parasite. Following immersion in hot saline solution (37 to 40°C) it was possible to observe that the cysticercus was induced to evaginate the neck and head proving that it was alive.

The other cyst was examined by optical microscopy. The histopathological findings revealed a tegument with three layers — an external cuticular, an intermediate nuclear and an internal parenchimatous — and in the interior the scolex having a double wreath of hooks characteristic of **Cysticercus cellulosae** [9]. Around the living parasite the inflammatory reaction was minimal or null, Fig. 2. The biopsy of the dermal nodules for macro- and microscopical examinations was repeated, 2, 4 and 12 weeks, after concluding the treatment to control the drug effect on the cysticerci.

Careful attention was paid to exclude patients having any clinical manifestations — decreased visual acuity, seizures, symptoms of intracranial hypertension, mental disturbances, signs of localized C.N.S. lesions — suspected of being caused by either ocular or brain cysticercosis. Moreover, all cases underwent ophtalmoscopic examination, skull X-rays, electroencephalogram recording and cerebrospinal fluid puncture. Immunological reactions for cysticercosis were performed in both serum and

Fig. 2 — Biopsy section from a subcutaneous cyst taken before treatment showing normal histology of the cysticercus within a fibrous capsule of host tissue

CSF[3,6]. The serological tests were repeated three months after completing the treatment.

Parasitological stool examination was made specifically to look for **Taenia** eggs. When positive, sieving a complete bowel discharge was carried out to identify the species (**Taenia solium** or **T. saginata**) through the inspection of the obtained mature proglotids. Except for the presence of **Taenia**, specific medication was administered before starting the praziquantel treatment. The stool examination was repeated one and three months afterwards in the positive cases.

Comprehensive physical examination with especial emphasis on the neurological condition was performed prior to therapy, every day during the treatment period as well as one and seven days after finishing the praziquantel administration. On these occasions the occurrence of adverse drug reactions was investigated and the spontaneously reported side-effects were recorded. The physical examination was repeated again on the 2nd, 4th and 12th week following the therapy when biopsy of the remaining dermal nodules were taken.

Hematological evaluation (complete blood counting and erythrosedimentation rate), urinalysis and blood biochemistry (alanin-, aspartat-aminotransferase, alkaline phosphatase, bilirubin and creatinine) were accomplished before as well as one and seven days after treatment to search into drug toxicity.

Fourteen cases had concomitant illnesses: severe paracoccidioidomycosis in two; two with mucocutaneous leishmaniosis, one moderate and one severe; malaria of moderate severity caused by **Plasmodium vivax** in two and; two with moderate anemia due to **Ancylostoma duodenale**. The others had less serious nosologic conditions. These pathologies were treated with specific medication prior to therapy with praziquantel.

RESULTS

In all patients the manometric values, cell count, total protein, glucose and chloride in the CSF were normal and the complement fixation and indirect hemagglutination tests for cysticercosis were negative. Fundoscopy, skull X-rays and EEG did not reveal any abnormalities.

Thirteen cases had positive stool examinations, 10 with helminthiasis but only in two caused by **Taenia solium** inspite that 10 patients reported to have noticed excretion of tapeworm fragments during the previous 12 to 30 months and all of them refered regular intake of rare porkmeat. The stool examination repeated 1 and 3 months after completing the therapy showed negative findings.

The therapeutical effect is demonstrated in Tables I and II. One may observe that the number of dermal nodules steadly diminished from an initial median value of 10 to zero at the end of 6 months following the treatment, as displayed in Fig. 1. Considering the mean number of nodules there was a decrease from 13.1 to 0.2 within this follow-up period or, as it is illustrated in Graphic 1, a reduction of 98.5%. Before therapy all cases had at least 8 nodules and 6 months afterwards 17 cases had none. The nodules persisted in 3 patients: in two, one with 34 and the other with 18 prior

TABLE I
Distribution of dermal nodules

Number of dermal nodules	Number of patients							
	Before treatment		After treatment					
			1 month		3 months		6 months	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
0	0	—	0	—	0	—	17	85.0
1	0	—	0	—	10	50.0	2	10.0
2	0	—	4	20.0	5	25.0	1	5.0
3	0	—	7	35.0	4	20.0	0	—
4 to 9	6	30.0	7	35.0	1	5.0	0	—
10 to 19	11	55.0	2	10.0	0	—	0	—
20 to 29	2	10.0	0	—	0	—	0	—
30 or more	1	5.0	0	—	0	—	0	—

TABLE II
Therapeutical response

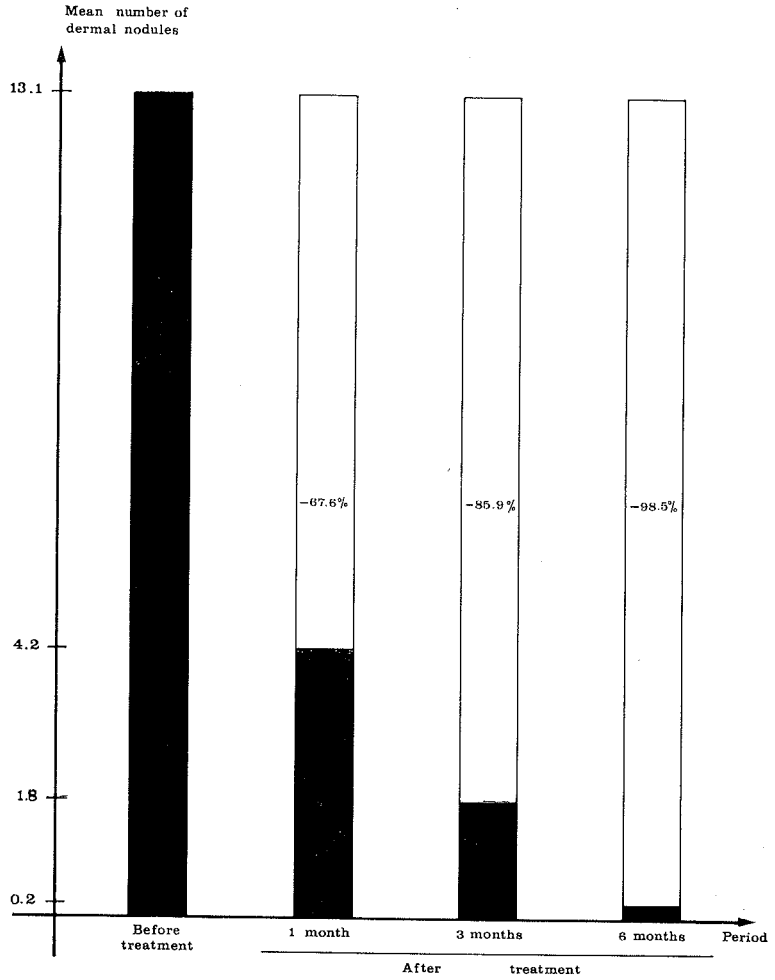
Number of dermal nodules	Before treatment	After treatment		
		1st month	3rd month	6th month
Total (in 20 cases)	262	85	37	4
Minimum	8	2	1	0
Maximum	34	10	5	2
Median	10	3	1.5	0
Mode	10	3	1	0
Mean	13.1	4.25	1.85	0.2
Reduction	—	67.6%	85.9%	98.5%

to the drug administration, there was a single remaining nodule and; one case initially with 25 had two nodules left. These remanent nodules were smaller and had a harder consistency than at the begining but they were still painless and moveable. Comparing 60 and 30 mg/kg/day no statistically significant difference was found between the two doses at the 6th month after therapy.

The biopsy taken two weeks after the end of treatment already revealed a disintegrated cysticercus. Macroscopically one sees a shrunk gelatinous cream-like mass of soft consistency. Looking through the microscope, the tegument is disrupted no longer making it possible to identify its three layers. Inside the vesicle the scolex is detached from the collum and deprived of hooks and suckers. The dead parasite is surrounded by a conspicuous lymphoplasmocitic inflammatory reaction with eosinophils also present Fig. 3.

One month after treatment the macro- and microscopic aspects are similar but the processes of degeneration and reabsorption of the cysticercus are more advanced and signs of chronic inflammatory and fibrotic reactions start to appear Fig. 4.

The biopsy repeated on the third month following the therapy shows the dead cysticercus reduced to a lenticular tuberculum of hard consistency. Under the microscope one obser-



GRAPHIC 1- REDUCTION OF DERMAL NODULES FOLLOWING PRAZIQUANTEL ADMINISTRATION

ves signs of chronic inflammation — fibroblast in radial arrangement and giant cells typical of foreign body granuloma — and fibrosis induced by the death of the parasite Fig. 5.

In the serum, prior to the treatment, the complement fixation was positive in 14 patients (mean and standard deviation, 7 ± 4.6 units) and the indirect hemagglutination in 12 patients (mean and standard deviation, 1: 163 ± 1: 159). In six cases both reactions were negative. On the third month after therapy the complement fixation continued to be positive in the same 14 cases but the mean value diminished to 1.1 ± 0.2 units. The indirect hemagglutination became negative in 5 cases and its mean titer decreased to 1.34 ± 1:9, Table III.

Regarding the occurrence of adverse drug reactions, only eight cases reported untoward effects. Abdominal pain or disconfort was the most common complaint (in 3 cases) then nausea (in 2) and vomiting, general malaise, dizziness, drowsiness, headache (in 1). These symptoms started during the first 3 days of drug intake and lasted for about 6 days. Whilst 7 patients treated with 60 mg/kg/day complained of side-effects, just 2 of those who received 30 mg/kg/day had complaints. However, there was no statistically significant difference between the tolerance of both doses, Table IV.

It was found no abnormalities in the laboratory results indicative of toxic praziquantel upon the hematopoietic liver and kidney functions.

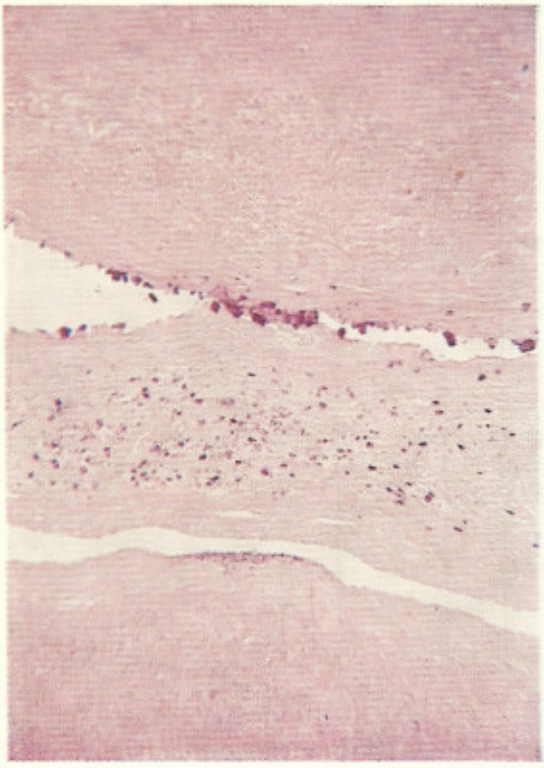


Fig. 3 — Biopsy section from a subcutaneous cyst taken two weeks after treatment showing a degenerate embryo and basement layer

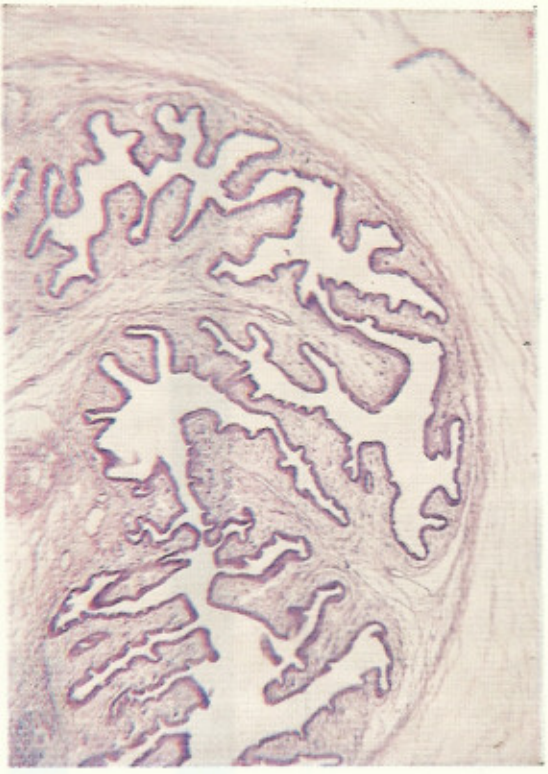


Fig. 4 — Biopsy section from a subcutaneous cyst taken one month after treatment showing a necrotic cysticercus containing numerous calcareous corpuscles

DISCUSSION

RIM [10] treated 20 patients with dermal cysticercosis including 8 presenting cerebral involvement as well. He administered 25 mg/kg t.i.d. for three consecutive days. Histopathological alterations on the subcutaneous cysts were observed two weeks following the therapy using an electron microscope. Most of the dermal nodules disappeared within the first 3 to 6 months. However, in a few cases, cysts were still found one year after treatment. Taking into account that his patients had a significant higher number of cysticerci (on average 42 in comparison to 13 in our cases) and that he used a different dose, both clinical experiences can be considered as concordant.

Our results lead us to the conclusion that praziquantel is highly efficacious for treating human cysticercosis caused by **Cysticercus cellulosae** localized in the subcutaneous tissue, a systemic parasitic disease in which, up to now, no other compound has proved its therapeutical efficacy. The death of the parasite can be detected already at the 2nd week following the treatment and the dermal nodules start to diminish in number and size form the 1st month on so that at the end of 3 months the majority of them has disappeared. The tolerance to the treatment is good considering that the incidence and severity of side-effects were not relevant. Moreover, the safety of the drug was demonstrated by the normality of laboratory findings and of the medical examinations performed during and after treatment.

RESUMO

Tratamento da cisticercose subcutânea com praziquantel. Um novo agente cestoidicida

Vinte pacientes adultos, com cisticercose subcutânea, sem associação com envolvimento ocular ou cerebral, foram tratados com praziquantel. Os primeiros 11 casos receberam 60 mg/kg/dia e os últimos nove 30 mg/kg/dia. Em ambos os grupos a dose oral diária foi dividi-

Fig. 5 — Biopsy section from a subcutaneous cyst taken three months after treatment showing a necrotic cysticercus surrounded by chronic inflammatory reaction and fibrosis

da em três tomadas, a intervalos de quatro a seis horas, e a administração do medicamento estendeu-se por seis dias consecutivos. O segundo grupo de pacientes tomou também dexametasona, 3 mg diários, desde um dia antes até quatro dias depois do período de tratamento com praziquantel.

A droga mostrou-se 100% eficaz como evidenciado histopatologicamente, pela morte da larva da **Taenia solium (Cysticercus cellulosae)** em biópsias seriadas, realizadas a partir da segunda semana após a terapêutica, bem como clinicamente, pelo paulatino desaparecimento dos nódulos cutâneos durante os seis meses seguintes ao tratamento. A tolerância ao praziquantel foi boa, tendo em vista a pouca relevância da incidência e da intensidade dos efeitos colaterais. A segurança do medicamento foi confirmada através de provas laboratoriais que não revelaram quaisquer anormalidades relativas às funções hematopoética, hepática e renal.

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TABLE III
Serum immunological findings

Reaction	Results	Before treatment	3 months after
Complement fixation	Positive	14 cases (70.0%)	14 cases (70.0%)
	$\bar{X} \pm \sigma$	7 ± 4.6 units	1.1 ± 0.2 units
	Minimum	3 units	1.0 units
	Maximum	20 "	1.5 "
Indirect hemagglutination	Positive	12 cases (60.0%)	7 cases (35.0%)
	$\bar{X} \pm \sigma$	1:163 ± 1:159	1:34 ± 1:9
	Minimum	1:80	1:20
	Maximum	1:640	1:40

TABLE IV
Drug tolerance

Patients / Assessment	60 mg/kg/day		30 mg/kg/day	
	No.	(%)	No.	(%)
Excellent	5	45.5	7	77.8
Good	5	45.5	2	22.2
Regular	1	9.0	0	—
Poor	0	—	0	—

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