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TREATMENT OF PARACOCCIDIOIDOMYCOSIS WITH KETOCONAZOLE

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SUMMARY

The results of the use of ketoconazole in 37 cases of paracoccidioidomycosis are presented. The drug was administered "per os" in the dose of 400 mg a day for 30 days and 200 mg a day for the following 60 days. With this treatment cicatrization of the cutaneous lesions occurred from 3 to 4 weeks in 32 patients and from 6 to 7 weeks in 4 patients. The direct mycological examinations became negatives in all cases. In 1 patient who had intestinal involvement without cutaneous lesions clinical improvement was registered. After the 90 days period of treatment the patients were divided in two groups. To the first one with 14 patients no further medication was given and to the second group with 23 patients was administered 200 mg of ketoconazole, three times a week. After a follow up period of 10 months a relapse was seen in 7 of 14 patients (50%) of the **Group I**, who were treated for only 90 days and in 2 of 23 patients (8.6%) of the patients of **Group II**, who received a maintenance dose of 200 mg three times a week. Ketoconazole is a very effective drug in the treatment of paracoccidioidomycosis, with excellent tolerance. It is the first choice in the therapy of paracoccidioidomycosis but the period of administration and the doses will need further studies.

INTRODUCTION

Prior to the 1940's and the advent of sulfa drugs [12] paracoccidioidomycosis carried out an almost hopeless prognosis. The sulfonamides are fungistatic drugs and must be administered for an indefinite period of time. Relapses occur upon cessation of therapy. In a review of 338 patients [15] treated between 1948 and 1958 with sulfonamides, 43% died of the disease and most of the survivors still had the disease. Amphotericin B was introduced in 1958 [5] and since then 400 patients have been treated with this antibiotic in our clinic with one or more series of amphotericin B. The review of these patients showed 51.0% with clinical and serological cure; 11.2% with clinical cure but with positive serology; 21.6% with clinical and serological activity of the disease; 16.2% of the patients died from the disease or related conditions, including in this group 2 patients who died from irreversible renal lesions. The nephrotoxicity of amphotericin B is the main toxic effect [1,2,3,8] of the amphotericin B.

Miconazole and clotrimazole, imidazolic derivatives have a topical action on superficial mycosis caused by dermatophytes or yeasts. They have a certain systemic activity in the deep mycosis but the published papers have not provided definite conclusions [4,6,7,9,10,11,13,14].

The research works carried out lead to the synthesis of a new imidazolic derivative, ketoconazole, presenting a better absorption by oral route in relation to the others which have already been studied and with excellent "in vitro" antifungal action. The present clinical trial aims to verify the action of ketoconazole in the treatment of paracoccidioidomycosis.

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MATERIALS AND METHODS

Ketoconazole, imidazolic derivative, is a white powder, slightly yellowish, practically odorless and tasteless. It was administrated by oral route in 200 mg tablets, in between meals without alkaline agents. This clinical trial was made in 37 cases of paracoccidioidomycosis. The diagnosis was based on the clinical aspects, direct and histopathological examinations. Radiological examinations were made according to the disease and complement fixation and precipitin reactions for paracoccidioidomycosis, (Fava Netto's tests) were performed.

The following tests were also made, before, during and after treatment: Complete hemogram, urea, creatinine, glycemia, cholesterol, total lipids, transaminases, protrombine, alkaline phosphatase, bilirubin and urinalysis.

In the 37 cases of paracoccidioidomycosis, 36 were males and 1 female; the mean age was 42 years and the disease's duration was from 2 months to 23 years. Of all 37 patients 24 have had previous treatments.

Of the 37 patients with paracoccidioidomycosis, 36 had skin lesions in which typical forms of parasites were found in the histopathological and direct examinations. In 1 patient there was no skin lesion. This patient had already been submitted to treatment and presented skin scars. The existence of intestinal signs of paracoccidioidomycosis showed through the radiological examinations as well as the positive results of the serological reactions justified their inclusion in the group. The precipitin tests were negatives in 18 and positives in 19 patients and the complement fixation tests were positives in 34 and negatives in 3 patients. Out of 37 patients, 23 presented a radiological pulmonary picture typical of paracoccidioidomycosis in activity.

In accordance with the clinical involvement, 13 patients had only tegumentary lesions, 23 had cutaneous-visceral lesions and 1 patient had only an intestinal involvement.

The 37 patients were divided into two groups: The first group of 14 patients received the ketoconazole for a period of 90 days, 400 mg a day for 30 days and 200 mg a day for 60 days. The second group, **Group II**, of 23 patients after the same dosage and period of time of treatment received a maintenance dose of 200 mg of ketoconazole, three times a week, for a period of 10 months. Both groups were followed with clinical, radiological, serological and other complementary examinations in this period of time.

RESULTS

After a period of 90 days of treatment with ketoconazole the 37 cases of paracoccidioidomycosis had the cicatrization of the skin lesions, which occurred from 3 to 4 weeks in 32 patients and from 6 to 7 weeks in 4 patients, with negative direct mycological examinations. The patient with intestinal involvement but without cutaneous lesion had clinical improvement. In according with the pulmonary lesions in the 90 days period of treatment, 1 patient had radiological remission and the other had improvement or unchanged X-rays. The clinical, radiological and serological results after 10 months of evolution are presented in Tables I, II and III.

The tables showed the following results:

Group I — In this group with 14 patients were observed 7 cases (50%) of relapses. Of these patients 2 had tegumentary forms, 4 had tegumentary-lymphatic-visceral forms and 1 had the intestinal form.

TABLE I

Results of the treatment with ketoconazole in a period of 10 months

Group I:	14 patients treated for 90 days (400 mg a day for 30 days and 200 mg a day for 60 days). Number of relapses: 7 (50.0%)
Group II:	23 patients treated with the same dosage for 90 days with a further maintenance dose of 200 mg of ketoconazole three times a week for 10 months. Number of relapses: 2 (8.6%)

TABLE II

Evolution of the pulmonary lesions (X-rays) in 23 patients

	Patients with lesions	Remission	Improvement	Unchanged	Undone
Group I	7	—	2 (28.3%)	3 (42.9%)	2 (28.6%)
Group II	16	1 (6.2%)	9 (56.2%)	4 (25.0%)	2 (12.5%)

TABLE III

Evolution of the serology in 10 months

	Precipitin tests			Complement fixation tests			
	Neg.	Dec.	Unch.	Neg.	Dec.	Unch.	Undone
Group I	8	1	1	3	6	1	4
Group II	11	2	5	—	15	3	5

Neg. : negative
Dec. : decrease
Unch.: Unchanged

Group II — In this group with 23 patients, who received the maintenance dose of 200 mg, three times a week, occurred 2 cases (8.6%) of relapses.

In accordance with the radiological pulmonary studies, 7 patients in the **Group I** with pulmonary lesions had the following evolution: in 2 there were improvement, in 3 the X-rays were unchanged and in 2 there were no further control.

In the **Group II**, of 16 patients with pulmonary involvement, the radiological studies showed disappearance of the lesions in 1 (6.2%), improvement in 9 (56.2%), unchanged aspects in 4 (25.0%) and without further control 2 patients (12.5%).

The serological evolution with the complement fixation and precipitin tests showed in **Group I** improvement or negativity in 4 patients unchanged in 1 and in 2 no further control. In the **Group II** there was negative precipitin in 11 patients, decrease in 2 and unchanged in 5. In this group, there was fall of the titers of the complement fixation tests in 15 and unchanged titers in 3. In 5 patients further serological tests were not performed.

COMMENTS

First of all the excellent results of ketoconazole in paracoccidioidomycosis must be pointed out. It has a therapeutic action comparable to amphotericin B. On the other hand, its excellent tolerance and ease of administration make ketoconazole the drug of choice for the treatment of paracoccidioidomycosis. It should be added that the drug was effective in patients resistent to sulfas and/or in those that had already undergone treatment with amphotericin B.

The 90 days period of administration of ketoconazole is not sufficient for the treatment since relapses occurred in 7 of 14 patients (50.0%). On the other hand the maintenance dose of 200 mg three times a week is also not sufficient since 2 cases (8.6%) of relapses occurred in the 10 month period of observation. The administration of 200 mg a day ketoconazole for a variable period of time in accordance with the clinical, radiological and serological evolution should be tried as the maintenance dosage in the therapy of paracoccidioidomycosis.

RESUMO

Tratamento da paracoccidioidomicose com ketoconazol

Os resultados do tratamento de 37 casos de paracoccidioidomicose pelo ketoconazol são apresentados. O medicamento foi administrado "per os" na dose de 400 mg ao dia por 30 dias e 200 mg por dia em 60 dias subseqüentes. Com este tratamento ocorreu cicatrização das lesões cutâneas em 3 a 4 semanas em 32 doentes e em 6 a 7 semanas em 4 doentes. O exame micológico direto das lesões cutâneas tornou-se negativo em todos os casos. Um dos doentes, apresentava exclusivamente comprometimento intestinal, tendo tido clinicamente melhora. Após 90 dias de tratamento os doentes foram divididos em dois grupos: o primeiro, com 14 doentes, não recebeu mais medicação e o segundo grupo, com 23 doentes, recebeu a dose de 200 mg de ketoconazol três vezes por semana. Após um período de 10 meses de seguimento, recidiva da moléstia foi registrada em 7 dos 14 doentes (50%) do primeiro grupo (50%) que foram tratados somente por 90 dias e em 2 dos 23 doentes (8,6%) do segundo grupo, que receberam a dose de manutenção de 200 mg, três vezes por semana.

Os Autores concluem que o ketoconazol é uma droga efetiva no tratamento da paracoccidioidomicose e com excelente tolerância. Poderá ser a primeira escolha no tratamento da mo-

léstia ainda que o tempo de administração e as doses do medicamento necessitarão de posteriores estudos.

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