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ACTION OF MICONAZOLE IN HISTOPLASMOSIS

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SUMMARY

The results obtained in 11 patients with chronic progressive forms of histoplasmosis are presented, the patients being treated with 3 g of miconazole per day by the oral route. The patients were all men. 10 Presented with mucosal lesions, 6 with pulmonary lesions, 2 with cutaneous, and in 5 cases the lesions were located elsewhere (adenomegaly, hepatosplenomegaly, and adrenal insufficiency). A clinical cure was obtained in 6 cases (54%), a marked improvement in 2 (18%), the treatment failed in 2 patients, and in one patient the results could not be evaluated because the treatment had to be suspended because of uncontrollable diarrhoea. With the exception of the later there were no side effects that could be attributed to the treatment. In our opinion, miconazole, a second-line drug, should be used in those cases where for various reasons sulphonamides or amphotericin B cannot be employed.

INTRODUCTION

Sulphonamide therapy has been used in Argentina in the treatment of histoplasmosis since the mid-1940's. Studies carried out recently 9, 11 have shown that the modern slowly-eliminated sulphonamides and the association of sulphamethoxazole with trimethopriam achieve a clinical and serological cure in the majority of patients suffering from this disease. Amphotericin B has also been used in our country, but to a smaller extent because of its toxicity, awkwardness of administration, and very high cost, being reserved mainly for patients allergic or resistant to sulphonamides 5. For these reasons we consider it interesting to test new drugs that might replace sulphonamides under such circumstances as described and which wou'd at the same time present fewer problems of toxicity and administration.

According to **in-vitro** studies, **Histoplasma capsulatum** is inhibited by miconazole at levels of 0.1-1 μg/ml culture medium[6,12], which places this fungus among those with the highest miconazole sensitivity. The excellent results obtained with miconazole in the treatment of paracoccidioidomycosis[7,10] encouraged us to test its therapeutic action in histoplasmosis.

MATERIAL AND METHODS

11 Patients were treated, all male adults, whose clinical data are given in Table I.

The diagnosis of histoplasmosis was based on the detection of **Histoplasma capsulatum** in biopsies of cutaneous-mucosal lesions in 10 cases and by a study of the sputum in 1 case. The samples were subjected to both mycological and histopathological tests.

We also carried out agar gel immunodiffusion tests and complement-fixation tests every 2 months from the start of the treatment. In these tests we used in **H. capsulatum** antigen prepared in accordance with the technique proposed by one of our group[4,8] and following the method recommended by the Pan-American Health Organization[2,3].

The complement-fixation tests were positive in 10 out of the 11 patients, with titres varying between 1/8 and 1/1024; the immunodiffusion tests were positive in 9 out of the 11 patients.

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TABLE I

Clinical data on patients with histoplasmosis treated with miconazole

Case No.	Initials	Age	Place of origin	Occupation	Localization				Period of evolution
					Mucosal	cutaneous	pulmonary	Others	
1	J.F.	57	Bs. As. prov.	...	+	—	+	suprarenal	2 years
2	C.S.	54	Entre Ríos	soldier	+	—	+	—	3 months
3	J.S.	72	Bs. As. prov.	farm worker	+	—	—	—	34 years
4	C.L.	52	Bs. As. prov.	policeman	+	—	—	ganglions hepatomegaly	11 years
5	J.M.	48	Bs. As. prov.	clerk	+	—	+	—	9 months
6	C.P.	44	Bs. As. prov.	clerk	+	—	—	ganglions hepatomegaly	6 months
7	A.C.	62	Bs. As. prov.	clerk	+	—	+	—	3 months
8	A.S.	43	Cap. Fed.	dyer	—	—	+	ganglions splenomegaly	2 years
9	A.K.	70	Misiones	businessman	+	+	—	ganglions	3 months
10	J.B.	34	Bs. As. prov.	farmer	+	+	+	—	5 months
11	G.C.	42	Bs. As. prov.	doctor	+	—	—	—	5 months

\+ yes
— no

Skin tests were carried out using histoplasmin L 48 (from the Mycology Centre of the Faculty of Medicine of Buenos Aires) diluted 1/100; these reactions were carried out simultaneously with the serological tests. The initial intradermal reactions were negative in 5 patients and positive in 6.

The following additional examinations were carried out every 30 days: ESR, blood picture, proteinogram, uraemia, creatininaemia, glycaemia, hepatogram, complete urine analysis, and chest X-ray.

Miconazole was administered orally in a dose of 3 g/day until a clinical cure had been obtained, the maintenance dose being 1.5 g for 6-12 months. The intravenous route was used in only one patient (J. F., case No. 1), the dose being 600 mg/day for 9 days.

The results of the treatment were classified as follows: a) very good, i.e. a clinical cure and no relapse for over 6 months; b) good, a clinical cure but follow-up examinations not continued for long enough, c) fair, a clinical improvement; d) poor, treatment failed, and e) result could not be evaluated due to intolerance resulting in suspension of the treatment before active levels could be obtained.

Two of the patients had previously received specific treatment; one with sulphonamides and the sulphamethoxazole-trimethoprim association and the other with amphotericin B; both had suffered relapses and the disease was active at the start of the miconazole treatment.

RESULTS

Table II shows the results of treatment with miconazole, the values shown being obtained at the last clinical and laboratory examination done for each patient.

TABLE II

Results of treatment with miconazole in patients with histoplasmosis

Case No.	Initial treatment	Maintenance treatment	Duration of follow-up	Side effects	Results
1	1 month	none	—	—	poor
2	1 month	none	1 month	—	good
3	2 months	7 months	1 year	—	very good
4	3 months	none	3 months	—	good
5	1 month	none	—	diarrhoea	not assessable
6	2 1/2 months	9 months	1 year	—	very good
7	2 months	1 year	1 year	—	very good
8	3 months	none	3 months	—	fair
9	16 days	—	—	—	poor
10	3 months	—	3 months	—	fair
11	1 1/2 months	—	1 1/2 months	—	good

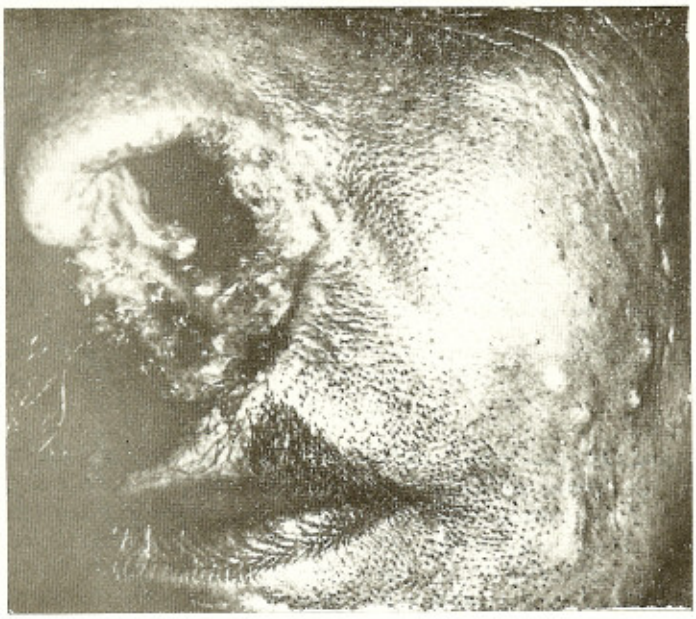

Fig. 1 — Ulcer of the nose and the upper lip, before treatment, patient No. 10.

Fig. 2 — The same lesion after treatment

The serological studies show no variations allowing the establishment of a correlation with the clinical evolution; it should be pointed out, however, that serological negativity was achieved in 1 case and in 2 patients the titre decreased.

The skin tests with 1/100-diluted histoplasmin were positive in 2 of the 5 histoplasmin-negative patients, as a result of treatment with miconazole, and in another 3 there was a strong increase in hypersensitivity.

The initial ESR was greater than 20 mm in the first hour in 7 patients, and in 4 there was a marked decrease, to less than half, after the treatment.

Study of the proteinogram showed γ-globulin levels greater than 1.30 g-% in 6 patients, later examinations showing variations that could not be related with the clinical evo'ution.

Five of the 6 patients with pulmonary radiological lesions showed marked improvement at subsequent examinations.

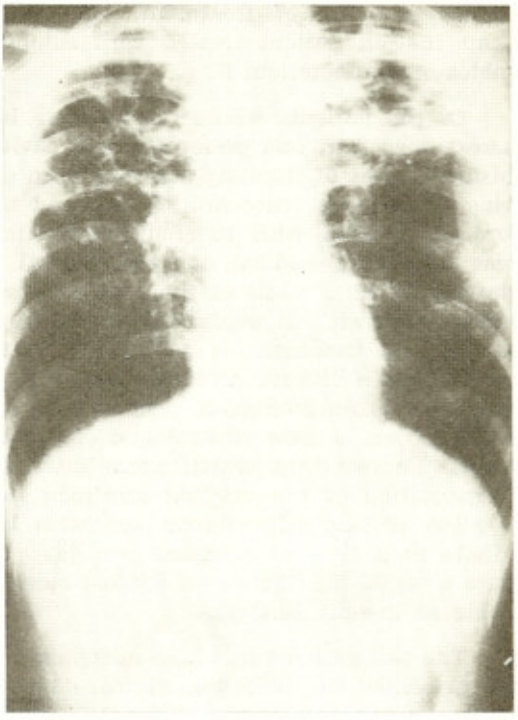

Fig. 3 — Preliminary cavitary lesion. Patient No. 8.

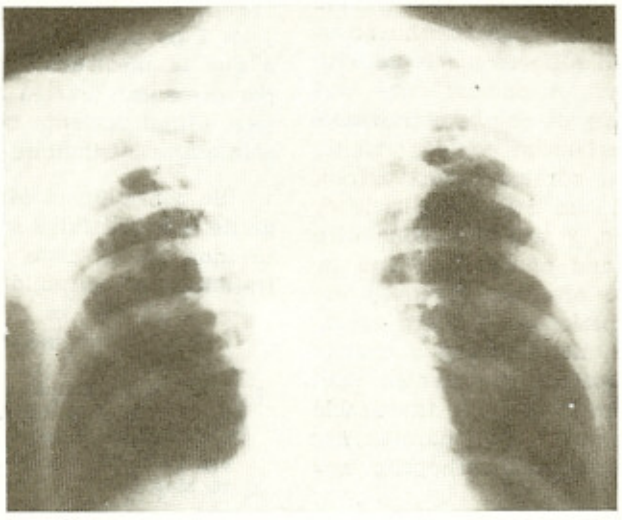

Fig. 4 — The same case after Miconazole

DISCUSSION

With the therapeutic scheme used we obtained 6 clinical cures (54%); these results were assessed as good or very good. Two patients presented marked clinical improvement (18%), in 2 the treatment failed (18%), and in the remaining patient the treatment had to be suspended owing to uncontrollable diarrhoea. The tolerance to the drug was excellent and only 1 patient with diarrhoea had to abandon the treatment.

In the cases which evolved favourably the clinical improvement was observed after 1

month or more of treatment, more slowly than that in patient treated with sulphonamides or amphotericin B.

Of the patients whose results have been assessed as fair, one presented with cavitary histoplasmosis of the lung that had been evolving for 2 years (case No. 8), and had been wrongly treated with tuberculostatics; there was a marked clinical and radiological improvement as a result of the treatment with miconazole, without achieving closure of the cavity; the treatment is continued. Patient No. 10 was a chronic alcoholic with very extensive mucosal-cutaneous lesions; this patient showed a slow clinical and histopathological improvement which necessitated supplementation of the original treatment with 1 g/day of sulphadimethoxin and with levamisole in a dose of 3 tablets per day three days a week. In this way a clinical cure was achieved in only 20 days.

The two patients in whom miconazole failed presented the following clinical data: Case No. 1 was a patient who suffered from chronic renal insufficiency, with grave disseminated histoplasmosis that had been evolving for 2 years; this patient had been treated with sufficient doses of sulphamethoxazole-trimethoprim and had suffered a relapse with adrenal insufficiency. A clinical cure was achieved with 3200 mg of sulphamethoxazole and 640 mg of trimethoprim per day; simultaneously he received adrenal cortex extract and levamisole, and the renal insufficiency was treated. Case No. 9 was a patient with lesions of the skin and of the oral and laryngeal mucosa, who after an apparent initial improvement experienced a sharp aggravation of the lesions, necessitating a change in treatment. This patient was treated with amphotericin B, after which a favourable evolution was observed; for maintenance therapy sulphamethoxazole-trimethoprim was indicated.

Even though the efficacy of miconazole in histoplasmosis is difficult to evaluate because of the relatively small number of patients analysed here, we have the impression that the therapeutic results are inferior to those obtained with sulphonamides and amphotericin B. In any event, having achieved 54% of clinical cures, we presume that by modifying the route of administration or increasing the dose the results could be improved. We consider that it would be useful to carry out tests with miconazole by the intravenous route, since this drug is known to have only alight adsorption by the digestive route [12].

Over-all, miconazole must be considered a second-line drug in the treatment of histoplasmosis. Its use would be indicated in those patients in whom sulphonamides or amphotericin B cannot be used.

RESUMEN

Accion del miconazol en la histoplasmosis

Se presentan los resultados obtenidos en 11 pacientes con formas crónicas progresivas de histoplasmosis, tratados con 3 gramos diarios de Miconazol por via oral. Los enfermos eran todos adultos del sexo masculino, 10 de ellos presentaron lesiones mucosas, 6 pulmonares, 2 cutáneas y en 5 casos se comprobaron otras localizaciones (adenomegalias, hepatoesplenomegalias e insuficiencia suprarrenal). Se obtuvo la curación clínica en 6 casos (54%), se observaron mejorías importantes en 2 (18%), en 2 pacientes el tratamiento fracasó y en 1 no pudo evaluarse el resultado debido a que la medicación debió ser interrumpida por presentar diarrea incontrolable. Salvo en este último paciente no se observaron efectos colaterales atribuibles al tratamiento.

Se considera al Miconazol, como una droga de segunda línea sólo empleable en los casos que por diversas razones no puedan ser tratados con sulfamidas o Anfotericina B.

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