

**TREATMENT OF SOUTH-AMERICAN BLASTOMYCOSIS  
(PARACOCIDIOIDOMYCOSIS) WITH ORALLY  
ADMINISTERED MICONAZOLE**

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**S U M M A R Y**

Miconazole (R-14.889) given orally demonstrated to be an efficient and potent chemotherapeutic agent for the treatment of South-American blastomycosis (paracoccidioidomycosis). The drug was used in 12 patients with active systemic and/or mucocutaneous involvement. The treatment period varied from 3 to 8 months and in all of the cases clinical cure was obtained. A post-therapeutic follow-up could be made in 9 of those patients. No relapses were demonstrated during a post-treatment observation period ranging from 3 to 15 months.

**I N T R O D U C T I O N**

The preliminary results obtained by the Authors with the use of orally administered miconazole (R-14.889) for the treatment of South-American blastomycosis were reported in a previous paper<sup>1</sup>.

This was a complementary communication aiming to confirm the satisfactory results in a larger number of patients and also to present a post-treatment observation of the cases during a period of up to 15 months.

**M A T E R I A L S A N D M E T H O D S**

Miconazole, imidazole 1- 2,4-dicloro-beta (2,4-dicloro-benziloxi), fenetil nitrate was administered to 12 in-patients (Hospital Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, R. J.) from July 1974 to November 1975.

All of the patients under therapeutical trial were Brazilians, 10 were males and 2 fe-

males, 7 white and 5 mulattoes and their ages varied from 34 to 65.

In two cases the infection was localized (cutaneous and/or mucocutaneous lesions with or without lymph node involvement). In the remaining 10 patients the infection was systemic, all of them showing pulmonary lesions.

In all 12 cases the lesions were active and the diagnosis of paracoccidioidomycosis was established through the finding of *Paracoccidioides brasiliensis* in mycological and/or histopathological examinations. Pulmonary tuberculosis was ruled out by repeated acid-fast stained smears and negative cultures for *Mycobacterium tuberculosis*.

In 10 patients there was no previous treatment specifically for this mycotic infection. From the remaining, one patient (case no. 12) had received sulfonamides and amphotericin B before, but relapses of the disease were frequent, while the other patient (case no. 6),

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also presenting relapse of the infection, had been previously under treatment with sulfonamides but for an insufficient period of time.

Miconazole 500 mg tablets were administered orally, in a daily dose of 3 g (1 g t.i.d.) to all patients of this series except to one (case no. 12) in which for the initial four weeks of treatment the first oral intake was replaced by an intravenous infusion of miconazole administered drop by drop (200 mg of miconazole diluted into 250 ml of a 5% glucose solution in distilled water).

The treatment period ranged from 3 to 8 months. When the patients showed healing of the lesions after a few weeks of treatment, it was established that the maintenance of the medication should continue for not less than a 4 month period. The only two exceptions on this schedule were due to a persisting side effect that could not be controlled (case no. 4) and in another patient the discontinuation of therapy was done without medical consent (case no. 8). In patients presenting extensive lesions and pulmonary involvement, the period of treatment was planned to continue until 2 months after the complete involution of the lesions, as determined by radiological and clinical examinations.

The following laboratory determinations were performed at fortnightly intervals, before, during and up to two months after completion of treatment: complete blood count (CBC), glucose, creatinine and cholesterol determinations in the serum, BUN, blood mucoprotein values, liver function tests (serum bilirubin, thymol turbidity, cephalin-cholesterol, glutamic oxalacetic and pyruvic transaminase tests) and urinalysis (abnormal chemical elements and microscopical examination of the urinary sediment). Also fortnightly an E.C.G. was taken and on patients with pulmonary lesions a chest X-ray was made every two weeks till involution of the lung lesions. In the post-therapeutic follow-up a chest X-ray was repeated every 3 months. In every patient serum protein electrophoresis was performed before the treatment and at monthly intervals during the therapy, while the patient was in the hospital, a daily clinical examination was performed and after the discharge clinical examinations were made in periodical medical visits to the out-patient clinic.

## CASE REPORTS

**Case no. 1** — M. F. T., a 62 year-old white housewife was admitted to the hospital in July 1974 and informed to be ill for 3 months. She presented lesions exclusively of the oral mucous membranes (cheek mucosa). Healing of the lesions was obtained after 4 weeks of treatment.

**Period of treatment:** 4 months

**Side-effects:** the patient complained of epigastralgia and nausea at the beginning of treatment but these symptoms disappeared with the temporary use of anti-acid and antiemetic drugs.

**Follow-up:** the patient was still clinically cured 15 months after the end of treatment.

**Case no. 2** — J.M.M., a 37 year-old white male, driver (formerly an agriculture worker) was admitted to the hospital in August 1974 and informed to be ill for 4 months. He presented cutaneous, oral (palate), pharyngeal, laryngeal and pulmonary lesions as well as lymph nodes (cervical) involvement. Involution of lung lesions was obtained after 4 months of treatment while the other lesions healed faster.

**Period of treatment:** 4 months

**Side-effects:** during the treatment the patient presented diarrhea that was easily controlled through the temporary and concomitant use of intestinal adsorbent drugs. He also presented occasional urticarial manifestations.

**Follow-up:** the patient still remained clinically cured for 9 months after finishing the treatment.

**Case no. 3** — W.D.S., a 54 year-old male, mulatto, agriculture worker, was admitted to the hospital in August 1974 and informed to be ill for one year. He presented involvement of the oral mucous membranes, lungs and lymph nodes (cervical and postauricular). Involution of the pulmonary lesions was obtained after 6 months of treatment while the other involved areas healed faster.

**Treatment period:** 8 months

No side effects were observed on this patient.

**Follow-up:** after the end of treatment in April 1975, the patient did not return for post-treatment examination.

**Case no. 4** — H. D., a 46 year-old white housewife was admitted to the hospital in September 1974 and informed to be ill for 9 months. She presented oral mucosa (tongue) and pulmonary lesions besides lymph nodes (cervical) involvement. Involution of lung lesions was obtained after 3 months of treatment while lymph nodes and involved mucosa became normal faster.

**Treatment period:** 3 months. The treatment was discontinued at the 3rd months due to uncontrolled side-effects.

**Side-effects:** during treatment the patient presented diarrhea that could not be controlled by conventional symptomatic drugs.

**Follow-up:** the patient still remained clinically cured 14 months after interruption of the therapy.

**Case no. 5** — J.R.F., a 63 year-old white male, agriculture worker was admitted to the hospital in October 1974 and reported to be ill for 5 months. He presented mucocutaneous (nasal vestibule) and pulmonary lesions. At the 5th month of treatment the patient left the hospital without medical consent, therefore interrupting medication. At that time mucocutaneous lesions were completely healed and the pulmonary involvement was much improved. No side-effects were observed and the patient did not return to the hospital anymore.

**Case no. 6** — B.F.M.S., a 44-year old male, mulatto, agriculture worker, was admitted to the hospital in January 1975. He said to be ill for 20 months and informed also to have been previously treated with sulfonamides for 4 months, obtaining healing of lesions. The patient stated that a few months after interruption of that medication there was relapse of the disease. At the moment of admission to the hospital he presented oral lesions (palate and cheek mucosa) and lymph node involvement (submaxillary and post-auricular). Healing of the oral lesions was obtained with 1 month of treatment with miconazole, but the

lymph nodes were still palpable at the end of this therapy.

**Period of treatment:** 4 months

**Side-effects:** During the treatment the patient presented diarrhea that was easily controlled with the temporary use of intestinal adsorbent drugs. The patient did not return for post-treatment follow-up.

**Case no. 7** — B.M.M., a 55 year-old male, mulatto, gardener, was admitted to the hospital in February 1975 and informed to be ill for 4 months. He presented laryngeal and pulmonary lesions. After 3 months of treatment there was healing of the lesions as shown by direct laryngoscopy and chest X-Ray examination.

**Period of treatment:** 5 months

**Side-effects:** The patient had diarrhea that was controlled by using intestinal adsorbent drugs.

**Follow-up:** the patient still remained clinically cured 4 months after completion of treatment.

**Case no. 8** — M.A.S., a 65 year-old mulatto, fisherman, was admitted to the hospital in March 1975 and informed to be ill for 5 months. He presented laryngeal, pulmonary and cervical lymph node involvement. The patient interrupted treatment and left the hospital without medical permission after three months of treatment. Although at that time the radiological examination showed marked involution of pulmonary lesions and a clinical improvement of the larynx could be detected, a definitive evaluation of the therapy could not be made in that occasion. The patient returned to the out-patient clinic 7 months later with different medical complaints and then a clinical and radiological examination revealed clinical cure of his mycotic infection.

No side-effects were observed.

**Case no. 9** — M.B.B., a 45 year-old white male, agriculture worker, was admitted to the hospital in March 1975. He presented cutaneous, oral (gums) and pulmonary lesions besides cervical and postauricular lymphadenopathy. Involution of the lung lesions was obtained after 5 months of treatment while the cutaneous and oral involvement healed much faster.

**Period of treatment:** 7 months

No side effects were observed.

**Follow-up:** The patient still remained clinically cured 4 months after completion of treatment.

**Case no. 10** — B.V.R., a 64 year-old white male, agriculture worker was admitted to the hospital in April 1975 and informed to be ill for 12 months. He presented oral (palate) and pulmonary lesions besides cervical lymph nodes enlargement. Involution of the lung lesions was obtained after 3 months of treatment while the oral lesions healed much faster. At the end of the therapy the involved lymph nodes were still palpable.

**Period of treatment:** 5 months

No side effects were observed.

**Follow-up:** The patient still remained clinically cured 5 months after completion of the treatment, but the involved lymph nodes were still enlarged enough to be palpable.

**Case no. 11** — B.M.S., a 56 year-old male, mulatto, agriculture worker was admitted to the hospital in May 1975 and reported to be ill for 18 months. He presented oral (lips and gums) and pulmonary lesions besides submaxillary lymphadenopathy. After 4 months of treatment there was involution of the lung lesions, while the other involved areas healed faster.

**Treatment period:** 6 months

**Side-effects:** During the treatment the patient presented diarrhea that was controlled with temporary use of intestinal adsorbent drugs.

**Follow-up:** the patient still remained clinically cured 3 months after completion of treatment.

**Case no. 12** — O.G., a 42 year-old white male, sawyer, was readmitted to the hospital in April 1975. Previously the patient had been hospitalized several times for treatment of South American blastomycosis and treated correctly with sulfonamides and amphotericin B. Relapses of lesions always occurred shortly after suspension of treatment. At the moment of this last readmission to the hospital he presented mucocutaneous (oral lips commissure) and pulmonary lesions and miconazole was the medication administered. During the initial 4

weeks of treatment the first oral daily dose of the drug was replaced by intravenous infusion of miconazole administered drop by drop. The pulmonary lesions subsided after 4 months of treatment while the mucocutaneous involvement healed completely in 15 days.

**Period of treatment:** 6 months

No side effects were observed.

**Follow-up:** the patient still remained clinically cured without relapses of the lesions, 4 months after finishing the therapy.

## RESULTS

In all of the patients of this series, miconazole orally administered led to complete cicatrization of cutaneous and oral, nasal, pharyngeal mucous membrane lesions in a period ranging from 2 to 6 weeks. The pulmonary and lymph node involvement subsided slower and in one case only after 6 months of treatment there was radiological evidence of complete healing of the lung lesions. In two patients the lymph nodes could still be palpable at the end of the therapy.

Side-effects were observed in 6 patients and they were always related to the digestive tract: 1 case of nausea and epigastralgia and 5 cases of diarrhea. These side-effects were easily controlled using anti-acid, antiemetic or intestinal adsorbent drugs. Only in one patient (case no. 4), because of persistent diarrhea, it was necessary to have a definite discontinuation of the medication at the 3rd month of treatment, when the lesions had already healed completely.

The laboratorial tests performed in all patients before, during and after treatment, to detect any toxic effects of the drug did not show any significant alteration of values. The serum protein electrophoresis and the blood mucoproteins that showed abnormal values before the treatment had a definitive trend to become normal in correlation with the clinical improvement of the patients, during the treatment.

The follow up of the patients after therapy (data computed up to January 1976) ranged from 3 to 15 months, in 9 patients. The re-

maining 3 did not return for post-therapeutic evaluation and from those, one (case no. 5) interrupted the treatment without medical consent, before completing the medication schedule prescribed.

The individual data concerning time of treatment and follow-up are listed in Table I.

T A B L E I

Time of treatment and follow up of 12 patients with South American blastomycosis treated with systemic miconazole

Case No.	Period of treatment (months)	Follow-up (months)
1	4	15
2	6	9
3	8	—
4	3	14
5	5	—
6	4	—
7	5	4
8	3	7
9	7	4
10	5	5
11	6	3
12	6	4

## DISCUSSION

In a previous paper<sup>1</sup> the satisfactory results obtained were shown with miconazole in the treatment of South American blastomycosis (paracoccidioidomycosis). Now, in a larger number of patients, with post-therapeutic follow-up, it is demonstrated that even when given orally miconazole is an efficient and potent drug, standing in the same level as amphotericin B and sulfonamides for the treatment of this systemic mycosis.

The use of miconazole in this series of patients confirmed its efficacy for the fast healing of the lesions of paracoccidioidomycosis and showed the persistence of the clinical cure after discontinuation of treatment, in all of the cases to whom the drug was administered. However, it has to be admitted that the post-therapeutic follow-up period in which these

patients were observed is still very short for a definitive evaluation, concerning the ideal extent of time in which the drug must be used, as well as, if miconazole would present further advantages over the conventional therapy for this mycotic infection.

An optimistic view for the advantages that miconazole could offer seems to be justified by the analysis of case no. 12 in this series. This was a patient presenting frequent relapses of lesions of South American blastomycosis in short periods (3 to 4 weeks) after completion of correct treatments with sulfonamides and amphotericin B. After using miconazole, his lesions were still healed 4 months after discontinuation of the drug.

With reference to tolerance to the medication, diarrhea was the only undesirable side-effect frequently observed, but it was easily controlled with symptomatic treatment and did not prevent the intake of the specific chemotherapeutic agent. The only exception occurred in case no. 4 in whom this side effect could not be controlled, therefore leading to the interruption of the treatment. In this patient that presented oral, pulmonary and lymph node involvement, it was possible to maintain the medication only for 3 months but a post-therapeutic evaluation 14 months later still showed persistence of her clinical cure.

It is of great interest to investigate the causes of diarrhea so frequently observed in patients receiving miconazole. It could be due to a local irritative action of the drug or to an unbalance of the intestinal flora through its antimicrobial action.

Regarding the toxicity of the medication, it remains the initial impression that the drug does not determine detectable alterations, at least through the exploratory methods that are usually utilized.

The final conclusion inferred through the analysis of the results obtained in the treatment of South-American blastomycosis with miconazole in a larger number of patients with post-therapeutic follow-up is that miconazole is not only an efficient but also a safe drug to be used in the treatment of this systemic mycosis.

### RESUMO

#### Tratamento da Blastomicose sul-americana (Paracoccidioidomicose) com miconazole administrado por via oral

Miconazole (R-14.889), administrado por via oral, demonstrou ser um agente quimioterápico potente e eficaz para o tratamento da blastomicose sul-americana (paracoccidioidomicose). A droga foi usada em 12 pacientes com envolvimento sistêmico e/ou mucocutâneo. O período de tratamento variou de 3 a 8 meses e a cura clínica foi obtida em todos os

casos. O acompanhamento pós-terapêutico foi possível em 9 pacientes. Durante o período de observação pós-tratamento, que variou de 3 a 15 meses, não foi observada nenhuma recidiva.

### REFERENCE

1. SANTOS-LIMA, N.; TEIXEIRA, G. A. & MIRANDA, J. L. — Tratamento da Blastomicose sul-americana pelo Miconazole oral. Resultados satisfatórios em 5 casos. *An. Brasil. Dermat.* 49: 245-251, 1974.

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