

SYSTEMIC MICONAZOLE TREATMENT OF A PATIENT WITH CHRONIC GRANULOMATOUS MUCOCUTANEOUS CANDIDIASIS

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Abstract. Miconazole given intravenously and orally was evaluated in the treatment of a patient with drug-resistant, chronic, widespread horny candida lesions. Marked clinical improvement occurred after 4 weeks of the first course of treatment, in which 400 mg of miconazole per day was given intravenously. After 3 months no signs of the disease were apparent. The patient remained free of symptoms for 3 months, after which the lesions recurred and a second course of treatment, with 200 mg of miconazole per day intravenously, was started. A prompt clinical clearing was seen within 3 weeks, after which the miconazole (1000 mg per day) was given orally. During oral administration of the drug a limited degree of recurrence of horny patches occurred. Systemic miconazole seems to be the drug of choice in the treatment of systemic chronic mucocutaneous candidiasis.

Key words: Miconazole; Systemic candidiasis

Miconazole is an imidazole derivative effective against gram-positive cocci and against most fungi and yeasts which cause skin or systemic symptoms (13, 14, 20, 26, 27, 32). The drug has been available since 1971, but commercial preparations only very recently. We describe here a case of drug-resistant chronic granulomatous mucocutaneous candidiasis treated by intravenous administration of miconazole, with good clinical improvement.

CASE REPORT

The patient was a 16-year-old boy who had suffered from *Candida albicans* infections since the age of 6 months. At 6 months he had occasional fever and cheilitis, continuously scaling scalp lesions, paronychia. His nails were dystrophic. *Candida albicans* was cultured from all of his lesions. In addition, a low hemoglobin level and low level of serum iron were found. He was treated successfully with topical antifungal therapy and with iron. Granulomatous hard horny lesions were first seen on the soles of his feet at the age of 3 years, when he was admitted to the hospital because of fever and oral thrush. A low level of iron was recorded, and the patient was therefore treated with topical antifungal drugs and iron. This treatment

brought all the symptoms under control but had no effect on the horny granulomatous patches. At the age of 5 years the patient had continuous cheilitis and granulomatous lesions on the soles. He was in poor general condition. *C. albicans* was cultured from the lesions of the mouth and soles. The patient received amphotericin B intravenously (319 mg/34 days). During this treatment all of the symptoms, including the horny patches, almost disappeared, but the treatment had to be discontinued because of the side effects, and new lesions were seen soon after the treatment was stopped. At the age of 6 years the patient had meningo-encephalitis. The spinal fluid showed high levels of protein, and increased numbers of cells, of which 99% were lymphocytes. *C. albicans* was cultured from the spinal fluid. The patient was treated with amphotericin B intravenously (760 mg/76 days). Within one month the spinal fluid was normal and the clinical symptoms had cleared, except for granulomatous candida lesions on the soles of his feet and at the corners of his mouth. During the amphotericin B treatment the candida granulomas were removed surgically from the soles. Amphotericin B was discontinued because of the side effects, and new lesions appeared soon after, on the borders of the skin grafts. From the age of 7 years, the patient had occasional cheilitis, oral thrush, and continuous horny patches on the borders of the skin grafts on his feet and at the corners of his mouth. In addition he had continuous paronychia and his nails were infected with candida. Candida was cultured numerous times from all of the lesions. The patient was treated continuously with topical antifungal and keratolytic therapy, with Nystatin orally, and with gammaglobulin injections every third week at the age of 10 years. At 11 years several horny lesions on the soles were removed surgically.

At the age of 12-13 years the patient received 7 injections of dialysable transfer factor from candida-positive healthy donors, but without any clinical improvement. Immunologic feature before and after transfer factor have been reported earlier (16). 5-Fluorocytosin was started at the age of 15 years. Ten days after initiation of the treatment the patient developed high fever combined with severe urticaria and the treatment had to be discontinued. Two weeks later provocation test with 5-fluorocytosin resulted again in urticaria, preventing the patient from receiving this therapy.

The patient was skin tested with *C. albicans* antigen on various occasions during the 12 years before miconazole treatment was initiated, 29 times with dilutions of 1:500

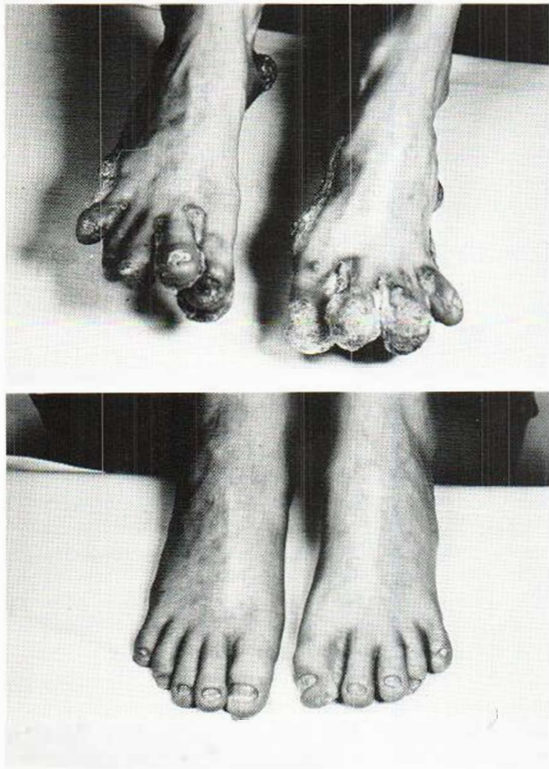


Fig. 1. Patient's feet before miconazole treatment and 2.5 months after the treatment was started.

and 1:50, and he always showed a negative skin test to candida. 12 years before miconazole treatment he showed a positive skin test to trichophyton (1:50), after which time the sensitivity was tested five more times, with no skin reactivity to trichophyton. The patient was sensitized with 10% dinitrochlorobenzene (DNCB) 5 years before the miconazole therapy and he became normally sensitized. His skin reaction to purified protein derivative of tuberculin (PPD) was always positive to 0.1–1 TU when tested six times during 12 years before the miconazole treatment. Positive skin reactivity to candida was seen after 3 of 7 attempts to transfer *C. albicans* sensitivity with dialysable transfer factor (TFd) prepared from healthy candida-sensitive donors (16), and acquired candida sensitivity was also demonstrated by the production of migration inhibition factor (MIF) to candida antigen in vitro (16). He received TFd injections for 337 days, the last occasion 2 years 2 months before the miconazole therapy was started. After the TFd injections the patient was skin tested with candida antigen five times during 2 years and was found to be negative to 1:500 and 1:50 of Dermatophytin "O".

Clinical and laboratory findings before miconazole treatment

The patient's weight was only 35 kg. He had horny lesions at the corners of the mouth, on the soles (Fig. 1), on the

palms, and around the nails (Fig. 1). The nails were dystrophic. Histological examination of the horny patches showed hyperkeratosis and acanthosis with a chronic inflammatory cell infiltrate in the dermis. Horny lesions on the soles prevented the patient from walking and the superinfections caused nauseous odour, both of which caused isolation and deep mental depression. *C. albicans* was cultured from all of his lesions (corners of the mouth, palms, soles, fingertips, skin around the nails). *Pseudomonas* was also cultured from all of these locations. In addition, bacteriological cultures showed superinfection by *Staphylococcus aureus* on the palms, fingertips, and skin around the nails, and by β -haemolytic streptococci and *Klebsiella aerogenes* on the soles.

The patient showed a negative skin test reaction to candida antigen (Dermatophytin "O", Hollister-Stier Laboratories, USA) at dilutions of 1:500 and 1:50 and to trichophytin (Hollister-Stier) at the same concentrations. He was positive to 1 TU of PPD (Statens Seruminstitut, Copenhagen) in the skin test and to 0.1% dinitrochlorobenzene (DNCB) to which he was sensitized with 10% solution. Electrophoresis, immunoelectrophoresis, levels of IgG, IgM, complement, and IgE were normal. IgA was low (0.45 g/l), and no specific IgE antibodies to *C. albicans* were found. Serum iron levels were normal and no other abnormalities were found in the laboratory examination.

Clinical and laboratory findings during miconazole treatment

During the first period of treatment, 400 mg of undiluted miconazole solution (Janssen Pharmaceutica, Beerse, Belgium) was given intravenously as a single dose every day for 3 months (Fig. 2). The treatment caused a dramatic clinical improvement and the patient was completely symptomless at the end of third month (Fig. 1). *C. albicans* could not be cultured from any of the sites in which it was present prior to the treatment. The patient was skin tested only 4 months after the miconazole therapy was started, when his skin test was strongly positive to 1:50 Dermatophytin "O" but negative to 1:500. During the therapy a slight decrease in hemoglobin and in the level of iron was noted, and iron therapy was instituted (Fig. 2). With numerous laboratory examinations, no other side effects could be detected. The only side effect was a daily skin rash for 3–4 hr starting shortly after the injection. This symptom started to appear 2 weeks after the miconazole treatment was started. However, as there was already a distinct clinical benefit from the treatment at that time, the miconazole therapy was continued and the rashes disappeared one week later (Fig. 2). When complete clinical improvement was achieved the treatment was discontinued. The patient remained free of any symptoms for a further 3 months. During this time he was skin tested with candida twice and showed no skin reactivity to Dermatophytin "O". After 3 months he started gradually to develop horny patches on his soles, and his nails became dystrophic again. After 5 months, horny patches were also seen on the palms and at the corners of the mouth. At this time a second course of miconazole treatment was started (Fig. 3). The dose was 200 mg daily intravenously. All the candida lesions healed within 3 weeks. One week later the

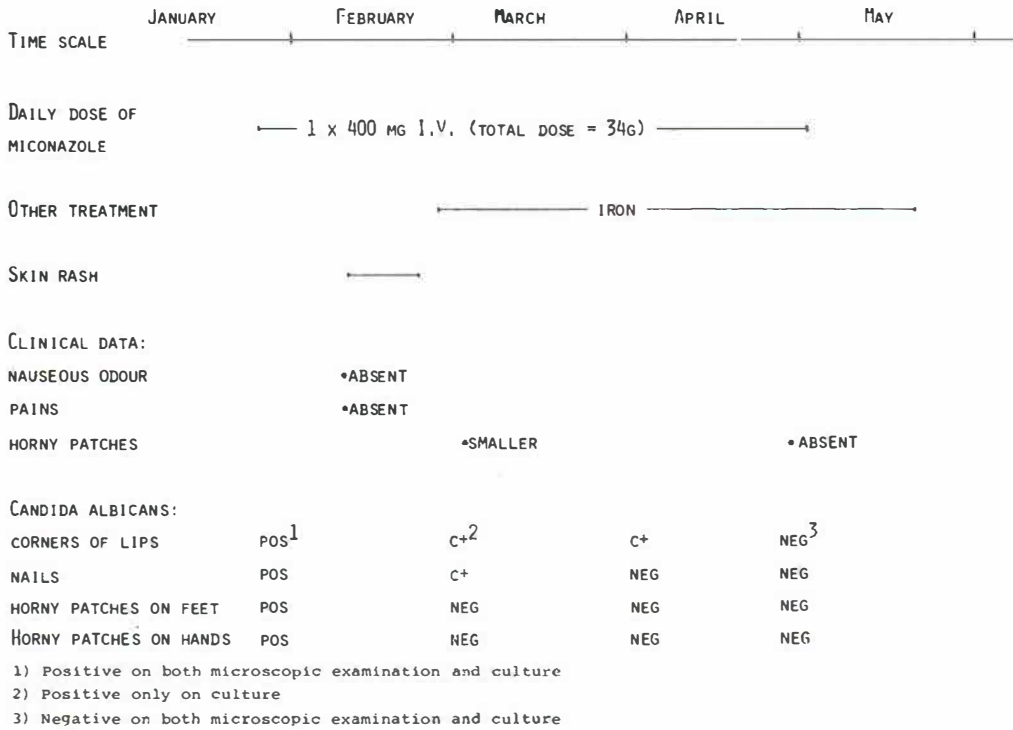


Fig. 2. The first course of miconazole treatment.

intravenous miconazole treatment was stopped and the treatment was continued orally (250 mg four times per day). This treatment was continued more than 3 months, during which a limited degree of recurrence of the horny skin lesions was seen. When skin tested one month after the treatment the patient was negative to candida in the skin test.

DISCUSSION

Cell-mediated immunity seems to be the primary barrier to fungus infections (reviewed in (1)).

Specific anergy to *C. albicans* in skin tests as reported in the present study, lack of candida-induced lymphocyte transformation, and lack of production of migration inhibition factor to candida in this patient (16) strongly suggest that a defect in cell-mediated immunity against candida was the primary cause of the widespread and chronic candidiasis in the present case. Amphotericin B treatment was used twice in the present case but had to be discontinued because of its toxic side effects. Nystatin

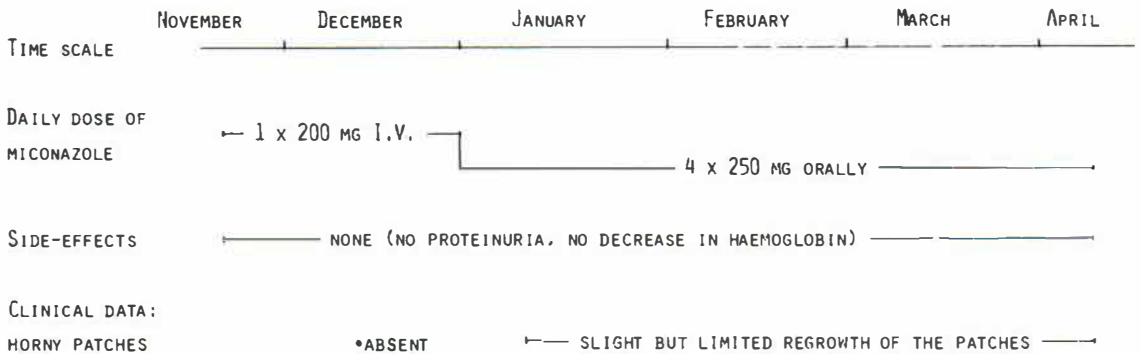


Fig. 3. The second course of miconazole treatment.

was also used for several years without success, and Tfd from candida-positive donors caused very painful local symptoms in the lesions and had to be discontinued (16). These considerations led us to treat the patient with a new drug, miconazole, which at that time was not commercially available for intravenous use. Miconazole has been used with good clinical results locally for candida infections of the skin, nails, and vagina (2-6, 8, 9, 11, 12, 18, 22, 25, 30, 31, 33), and orally and intravenously for systemic candidiasis (10, 17, 19, 21, 23, 24, 28, 29, 34, 35). Several topical treatments, including amphotericin B in the local therapy in the present patient, had proved unsuccessful, probably because of the limited penetration of the drug through the horny lesions. We therefore chose to use miconazole systemically. According to their sensitivity to miconazole the systemic mycoses have been divided into two classes (29). The most sensitive fungi are South American blastomyces, blastomyces and histoplasma, and less sensitive are candida, cryptococcus and coccidioides. Fungi of class 2 are inhibited by miconazole at concentrations of 1 to 10 $\mu\text{g/ml}$ in vitro (29). If similar blood levels are necessary for in vivo inhibition, systemic candidiasis should be treated with intravenous miconazole, in which blood levels have been found to be between 1 and 10 $\mu\text{g/ml}$ in most patients (13, 27, 29). The results of the present study support this conclusion, since only intravenous miconazole treatment was effective for complete improvement of candida lesions. However, miconazole administered orally also kept the lesions within clinically acceptable limits, although there was a limited degree of recurrence of the horny lesions. On the other hand, the doses generally used for intravenous infusion have varied between 600 and 1400 mg daily (29). Although the weight of the patient was taken into account, the dose of miconazole at least during the second course of treatment (Fig. 3) was low but was still effective. Skin rash was the only side effect during the treatment. No other side effects (chills, dizziness, itching, diarrhoea, loss of appetite, nausea, vomiting, or transient increase in serum lipid levels) (29) were observed, which is in accordance with most reports showing that side effects of the drug are very rare and that miconazole can safely be given to seriously ill patients (2, 10, 17, 19, 21, 23, 24, 28, 29, 34, 35). The mechanism of action of miconazole on *C. albicans* is not completely known. It has been sug-

gested that miconazole inhibits the peroxidative enzymes cytochrome C peroxidase and catalase, thus resulting in peroxidase accumulation and cell necrosis (7).

For 2 years after the last injection of Tfd the patient had shown negative skin tests to candida on many occasions. Interestingly, a positive skin test to candida was seen at the end of the first course of the miconazole treatment without a new Tfd injection. The acquisition of skin reactivity by effective antituberculosis treatment of a tuberculin-negative patient with lupus vulgaris without a new injection of Tfd has been reported previously (15).

It appears that miconazole is a highly effective drug in systemic candidiasis, is atoxic, and has few side effects.

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Received January 7, 1978

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