

MICONAZOLE IN THE TREATMENT OF CANDIDIASIS OF THE DIGESTIVE TRACT

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Abstract. Miconazole nitrate tablets were used in the treatment of candidiasis of the oral cavity and the digestive tract. In 5 out of 6 patients with severe, predisposing factors and who had received previous unsuccessful antimycotic therapy, clinical improvement occurred after a few days of miconazole treatment. Mycological cure of these 5 patients was achieved after 1–11 weeks of treatment. Three of the 5 cured patients relapsed after 3 months, due to basic failure. One patient complained of the drug's unpleasant taste. Otherwise, no side effects were observed. There was no apparent development of any resistance to the drug.

Key words: Miconazole; Candidiasis; Digestive tract

Miconazole nitrate (Brentan®)—an imidazole derivative with the chemical formula: 1-[2,4-dichloro- β -(2,4-dichlorobenzoyloxy) phenethyl] imidazole nitrate—has been described as a reliable broad-spectrum antimycotic drug (3) active in such fungal infections of the human skin as dermatophytosis, candidiasis and pityriasis versicolor (1, 6, 8). Furthermore, vulvo-vaginal candidiasis has been treated with miconazole with success (5, 7). Obviously, it would be of interest to test the drug against other mucosal candida infections, such as those of the oral cavity and the entire digestive tract.

Miconazole has been found to be non-toxic and is scarcely absorbed at all from skin or mucosal membranes (2). After oral administration, the drug is absorbed moderately well, and prolonged treatment with 1 g miconazole nitrate daily produces serum concentrations of 0.5–1 g/ml, a concentration considered to be without antifungal activity (4).

Candidiasis of the oral cavity, oesophagus, gastric and intestinal mucosa is frequently observed

together with a variety of disorders and diseases other than malignancy. For instance, patients wearing dentures often get a fungal stomatitis both with and without symptoms. Furthermore, treatment with systemic steroids, immunosuppressive therapy and/or broad-spectrum antibiotics may result in candidiasis of the mucosa of mouth and digestive tract. Finally, persons with congenital immunodeficiencies are often found to have chronic candida infections necessitating constant antimycotic therapy.

MATERIAL AND METHODS

This study comprises 6 patients aged 2–54 years with candidiasis of the oral, pharyngeal, oesophageal and/or intestinal mucosa. They were all severely predisposed and had previously been treated with other antimycotic drugs with variable success.

A clinical and mycological examination took place before, during, at the end of and after the treatment. The investigations were carried out at one- or two-week intervals during the first month of treatment and then at four-week intervals until an average of 8 months after treatment was concluded (range: 3–12 months).

The mycological study involved microscopy of scrapings from the tongue, oral and/or pharyngeal mucosa. The material was cleared with potassium hydroxide 30% and cultured on Sabouraud dextrose agar with penicillin and streptomycin. For further isolation of *Candida albicans*, corn-meal agar was used. Isolation of other *Candida* species and examination of stools were performed at the mycological department, Statens Seruminstitut.

Miconazole nitrate was given as tablets of 250 mg in doses of $\frac{1}{2}$ –1 tablet 3–6 times daily. The tablets were allowed to melt in the mouth and then swallowed. For patient 1 the tablets were crushed, dissolved in water and given with a spoon. The duration of treatment varied as shown in Table 1, in which all the most important data including the mycological findings are presented.

Table 1. Clinical findings in 6 patients with candidiasis and results of mycological examinations before and after treatment with miconazole (Mic)

Case	Sex	Age	Underlying disease/ predisposing factors	Duration of candidiasis	Location of candidiasis	Mic. treatment	
						Dosage	Duration (weeks)
1	♂	2	Histiocytosis X. Broad-spectrum anti- biotics. Prednisone	4th infection in 6 months	Gut	125 mg × 4	12
2	♂	34	Klinefelter syndrome. Dentures	2 years	Mouth	250 mg × 4	4
3	♂	38	Dentures	1½ year	Mouth	250 mg × 4	4
4	♀	54	Hypertrophic lanuginosa acquisita. Dysplasia of papilli fungiforme	1 month	Mouth, gut	250 mg × 4	6
5	♀	24	Systemic lupus erythematosus. Prednisone, Imuran, Antibiotics	2 months	Mouth	250 mg × 6 for 10 days 250 mg × 4	4+5
6	♂	7	Congenital immunodeficiency (humoral and cellular)	7 years	Mouth, oesophagus	250 mg × 4 for one month 250 mg × 3	Continu- ously

CASE REPORTS

Case 1

A 2½-year-old boy, who, since the age of 14 months, suffered from exudative seborrheic dermatitis of the skull and ano-genital region. Since the age of 2 years, he had frequent infections: impetigo, otitis externa and media, and broncho-pneumonia, all of them adequately treated with broad-spectrum antibiotics (dicloxacillin sodium, ampicillin) which were followed by diarrhoea from which colonies of *Candida albicans* in pathological amounts were cultured. The skin affection was highly recalcitrant and this together with the frequent infections led to further examinations. X-ray examination of the skull, and ophthalmological and histological examination revealed an eosinophilic granuloma (Histiocytosis X) of the left parietal region and ear-tube. This was treated surgically and with systemic corticosteroids.

The candidiasis of the intestines was treated twice with nystatin for 3 weeks, both times with recurrence of the diarrhoea after one week. Miconazole treatment was initiated at the same time as the systemic steroid and lasted for 3 months, at which time antibiotic treatment too, was stopped. No relapse was observed although the systemic steroid treatment was continued for several months.

Case 2

A 33-year-old male with Klinefelter's syndrome. For 2 years he had suffered from severe candidiasis of the mouth secondary to a bad dental condition. Extraction of most of the teeth did not improve the situation, neither did an ill-fitting denture. Topical treatment with nystatin and amphotericin B did not improve the candida infection.

Before treatment with miconazole, redness of the oral mucosa and thick creamy membranes were observed, and the patient complained of severe burning and difficulty in eating solid food.

After 3 days of treatment with miconazole, clinical improvement was obtained and after 8 days there was clinical and mycological cure. Six weeks after the treatment a positive culture with *Candida tropicalis* and *Torulopsis glabrata* was obtained, but clinical symptoms of reinfection did not start until 3 months later.

Case 3

A 38-year-old male who suffered from oral candidiasis for 18 months. Treatment with amphotericin B topically for 6 weeks and nystatin for several months was unsuccessful.

Clinical examination revealed an erythema over the entire oral mucosa and tongue, and widespread creamy membranes. The teeth of the upper jaw had been extracted and, corresponding to the canine teeth, two metal projections had been inserted in order to support a denture. Around these projections the mucosa was very red and oedematous. Treatment with miconazole nitrate resulted in clinical improvement within a few days and mycological cure after 2 weeks. Because of a relapse 3 months later, the treatment with miconazole was repeated, combined with surgical reconstruction resulting in complete cure.

Case 4

A 54-year-old female with candidiasis of the mouth and intestines secondary to a symptom complex consisting of diarrhoea, loss of weight and hypertrophic lanuginosa acquisita. The latter symptom has been described earlier

Mycological findings

Before	During	After treatm.
<i>C. albicans</i> 50-100 col.	Neg. after 11 weeks	Neg. 6 months later
<i>C. albicans</i> >100 col.	Neg. after 1 week	<i>C. tropicalis</i> + <i>Tor.</i> <i>glabrata</i> 6 weeks later
<i>C. albicans</i> >100 col.	Neg. after 2 weeks	<i>C. albicans</i> 3 months later
<i>C. norve-</i> <i>gensis</i> >100 col.	Mouth: 5 col. after 3 weeks, 50-100 col. after 4 and 6 weeks. Stools: neg. after 3 weeks	<i>C. norvegensis</i> , <i>Tor.</i> <i>glabrata</i> + <i>C. para-</i> <i>psilosis</i> continu- ously
<i>C. albicans</i> 50-100 col.	Neg. after 2 weeks neg. after 5 weeks	<i>C. albicans</i> 3 months later
<i>C. albicans</i> 50-100 col.	25-50 col. after 3 weeks neg. after 8 weeks	

in relation to a malignant disease. In fact, a cancer of the right breast was diagnosed subsequently.

The treatment of the candidiasis of this patient was unsuccessful; there was no clinical improvement at all, though the mycology showed a reduction in the number of colonies. This patient was the only one in the present study who complained that the tablets had a bad taste.

The oral mucosa in this case was very red and the tongue showed severe pathological changes of the fungiform papilli, with deep clefts in between. No membranes were seen.

Case 5

A 24-year-old female suffering from systemic lupus erythematosus for 10 years. Therapy with corticosteroids and intermittent treatment with cytostatics and antibiotics was given for several years.

The first attack of candidiasis was in 1969, located in the mouth; the second in 1972, located in the vagina. Both were successfully treated with nystatin. In 1973 she developed candidiasis of the tongue and the oro-pharyngeal cavity.

Treatment with nystatin for one month gave no improvement. Miconazole was given for 4 weeks (250 mg $\times$ 6 daily for 10 days, then 250 mg $\times$ 4 daily). On account of a relapse after 1 week the treatment was repeated. The symptoms disappeared both times about 3 days after starting the treatment. A relapse occurred 3 months after the last treatment.

Case 6

A 7-year-old boy with congenital humoral and cellular immunodeficiency. Since birth he had had frequent in-

fections with both bacterial and fungal pathogens. He had been on constant antibiotic and antimycotic treatment (nystatin, amphotericin B, clotrimazol) all his life. The basic deficiencies were treated with gamma-globulin, and subsequently transfer factor was tried. From the outset the fungal infection caused by *Candida albicans* affected both the skin and the mucosa of the oral cavity and oesophagus. Just prior to treatment with miconazole, the most distressing symptoms were those from the mouth, pharynx and oesophagus which for 2 years caused difficulties in swallowing solid food. Thick membranes of thrush were seen on the tongue, and oral and pharyngeal mucosa. An X-ray photo of the oesophagus revealed a stricture in the distal part.

Miconazole was given in a dose of 250 mg $\times$ 4 daily for one month, followed by 250 mg $\times$ 3 daily. After one month the symptom were so far alleviated that the patient was able to eat white bread and, after 6 months, normal food was well tolerated.

Mycological cure was obtained after 6 weeks. The patient was continuously treated with miconazole, as the basic failure seemed to necessitate constant antimycotic as well as antibiotic treatment.

RESULTS AND COMMENTS

Complete clinical and mycological cure was obtained in 5 out of 6 patients. In 3 of these cases (nos. 2, 3 and 5) clinical relapse occurred about 3 months after discontinuation of the treatment, due to the underlying predisposing diseases. In case 3, where this basic failure was subsequently eliminated, the candidiasis did not recur within one year of follow-up after a second treatment with miconazole. Concerning patient no. 6, who is still undergoing treatment, it is remarkable that no resistance of *C. albicans* to the drug has yet been observed.

In case 4 no cure was obtained. The species found was *C. norvegensis*, a subvariety of *C. zeylanoides*. The sensitivity to miconazole of this species has more recently been assessed in vitro and the pathogen found moderately sensitive. This observation indicates possible resistance as the reason for clinical failure. Furthermore, the severe dysplastic changes of the tongue may have caused incomplete penetration in this patient.

CONCLUSION

Miconazole is a highly effective drug in the treatment of candidiasis of the digestive tract. The clinical effect sets in very quickly, and the drug is well tolerated. Consequently, miconazole may be considered a valuable new drug in the treatment of candidiasis. It may be of particular interest that the

drug was effective in fungal denture stomatitis, a disease known to be resistant to other forms of treatment.

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REFERENCES

1. Botter, A. A.: Topical treatment of nail and skin infections with miconazole, a new broad-spectrum antimycotic. *Mykosen* 14 (4): 187, 1970.
2. Brugsmans, J., Cutsem, J. van, Heykants, J., Schurmans, V. & Thienpont, D. C.: Systemic antifungal potential, safety, biotransport and transformation of miconazole nitrate. *Europ J Clin Pharmacol* 5: 93, 1972.
3. Cutsem, J. van & Thienpont, D. C.: Miconazole, a broad-spectrum antimycotic agent with antibacterial activity. *Chemotherapy* 17: 392, 1972.
4. De Broe, M.: Antifungal activity of blood of patients chronically treated with miconazole. Janssen Research Products Inf. Service. Sec. 10, no. R 14889/16, April 1972.
5. Godts, P., Vermeyhen, P. & Cutsem, J. van: Clinical evaluation of miconazole nitrate in the treatment of vaginal candidiasis. *Arzneim Forsch* 21: 256, 1971.
6. Svejgaard, E.: Double-blind trial of miconazole in dermatomycosis. *Acta Dermatovener (Stockholm)* 53: 497, 1973.
7. Thiery, M., Mrozowski, P. J. & Kets, H. van: Miconazole, a new broad-spectrum antimycotic, in the treatment of vaginal candidiasis. *Mykosen* 15 (1): 35, 1972.
8. Thulin, H. & Østerby, P.: Miconazole in the treatment of dermatomycosis. *Mykosen*, unpubl. data.

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