CASE REPORTS

Refer to: Sung JP: Treatment of disseminated coccidioidomycosis with miconazole. West J Med 124:61-64, Jan 1976

Treatment of Disseminated Coccidioidomycosis with Miconazole

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SINCE 1956, amphotericin B has been established as an effective drug for the treatment of various systemic mycotic infections. Unfortunately, its effectiveness has been hampered by its untoward side effects or toxicity.[1,2] Since the condition of the patient discussed in this report was deteriorating from the disease and side effects of amphotericin B, treatment was begun with miconazole, a synthetic 1-phenethyl-imidazole derivative.[3] The drug appears to be safe, with broad-spectrum antifungal activity.[4,5]

Report of a Case

A 50-year-old black man came to the San Joaquin Valley from Louisiana in 1970. He worked in a cotton field until March of 1973 when he started work in a grain mill. He was in good health until five months later when he began to tire easily. In October 1973, cough, night sweats, anorexia, fatigue, weight loss and occasional chest pain developed. Despite three months of treatment with antibiotics and lancing of the abscesses by his private physician, his condition progressively deteriorated, the patient lost more than 40 pounds and new abscesses continued to develop.

The patient was first admitted to the Fresno Veterans Administration Hospital on January 21, 1974. The abnormal physical findings were confined to the skin and subcutaneous tissues. Several tender nodules of various sizes, the largest measuring 6 cm in diameter, were found on the right shoulder, left flank, upper arms, right hip, upper thighs and left upper lip. There were also several healed scars from previous lanced abscesses. The temperature taken orally was 39.4°C (103°F), and pulse was 100 per minute. The lungs were clear, except for a few rhonchi at the bases. The remainder of the physical findings were normal.

Findings on x-ray studies of the chest, right shoulder and hips included no abnormalities. The hemoglobin was 11.2 grams per 100 ml, hematocrit 37 percent, leukocyte count 19,800, with 93 percent neutrophils. Blood urea nitrogen was 7 mg per 100 ml, serum creatinine 1.0 mg per 100 ml and liver profile normal. Results of coccidioidin skin tests were negative at 1:100 and 1:10 dilutions on repeated examinations. Findings on a coccidioidal spherulin skin test were also negative. Direct smear from the abscesses yielded spherules of Coccidioides and culture grew typical colonies of Coccidioides immitis. On biopsy of the fungating upper lip lesion, a coccidioidal granuloma was noted. The complement fixation titer was 4 plus at a dilution of 1:125.

Despite therapy with amphotericin B given intravenously, abscesses continued to develop that required frequent incision and drainage. Temperature ranged from 38.3°C (101°F) to 40.6°C (105°F) for 80 days. Leukocytosis with a left shift persisted. After four weeks of amphotericin B therapy, the blood urea nitrogen rose from 7 to 55 mg, and the serum creatinine from 1.0 to 2.8 mg. Both values returned to normal when the drug was discontinued and the dosage schedule modified. During amphotericin B treatment, the patient experienced headache, nausea, vomiting, anorexia, chills and fever. A total of 2.25 grams of amphotericin B was given during a 90-day period. During the last two weeks of therapy, the patient's general condition improved with only one small nodular lesion remaining on the right shoulder. He was discharged from the hospital on April 23, 1974, to be followed in the Outpatient Clinic.

The patient was readmitted to the hospital on August 26, 1974, with severe pain in the right shoulder and a recurrent tender coccidioidal ab-

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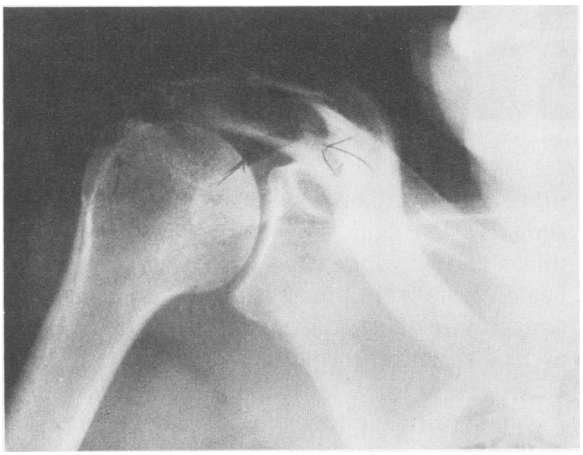

Figure 1.—Destructive lesions of scapula and acromion, and greater tuberosity of humerus of right shoulder despite administration of amphotericin.

scess on the right side of the neck. One month before admission, the patient stated he had had periodic chills and fever. On physical examination, diffuse tender swelling over the right shoulder and a fluctuant mass on the right side of the neck were noted. The temperature taken orally was 38.5°C (101.3°F), lungs were clear and findings on an x-ray film of the chest were normal. However, on an x-ray study of the right shoulder, bone destruction of the right scapula and right acromion and greater tuberosity of the right humerus were noted (Figure 1). Erythrocyte sedimentation rate was 38; leukocyte count 17,800 with shift to the left; hemoglobin 12.6 mg per 100 ml, and levels of serum bilirubin, alkaline phosphatase, serum glutamic oxalic transaminase and lactic dehydrogenase were

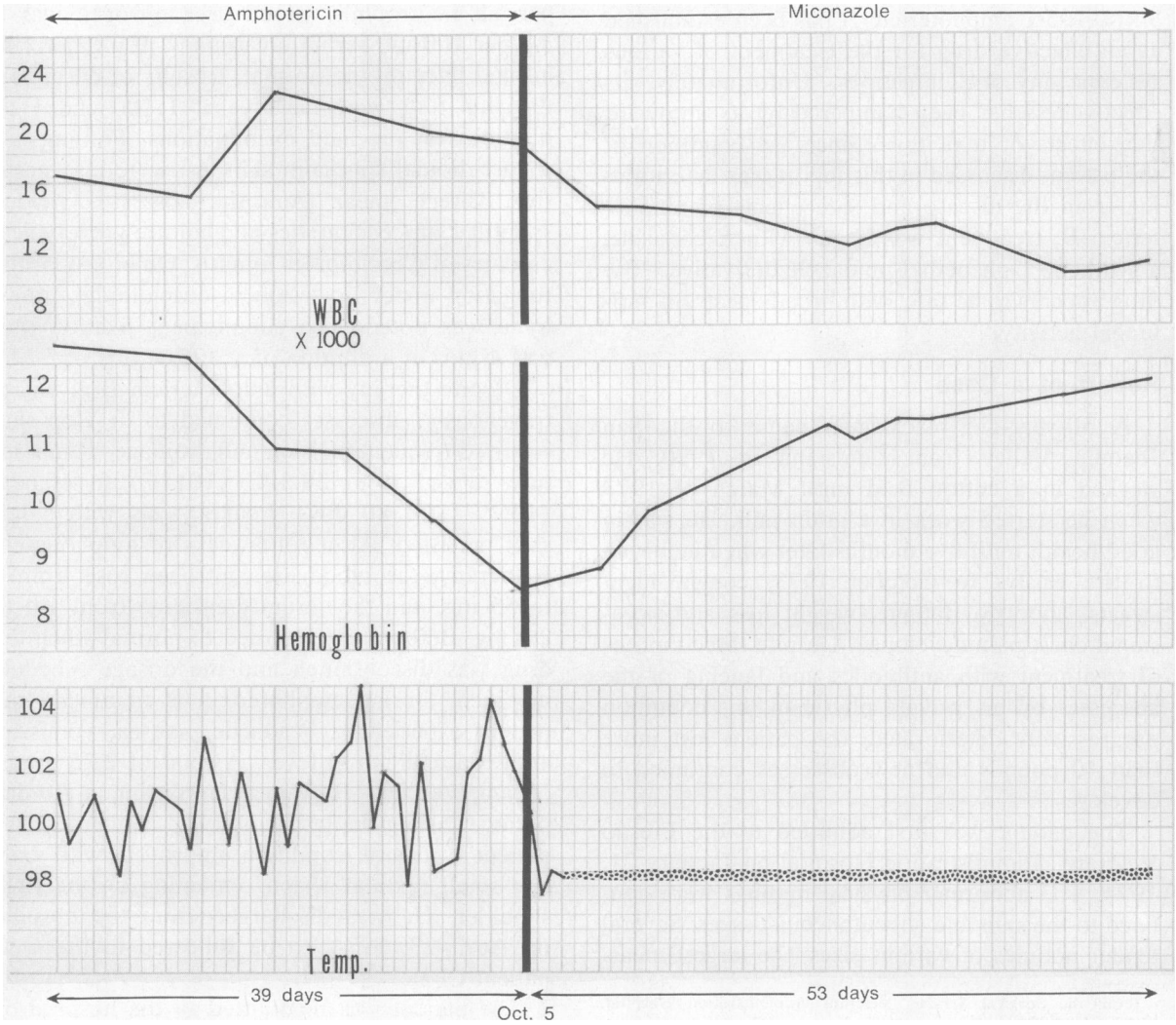

Figure 2.—Comparative clinical course during amphotericin and miconazole therapy. (WBC indicates leukocyte count.)

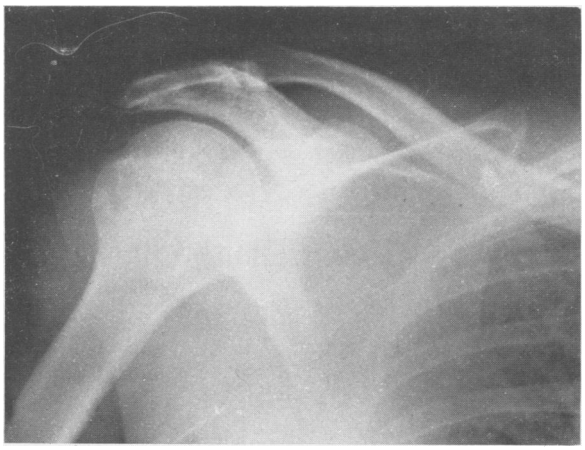

Figure 3.—Healing of bony lesions of right shoulder after six weeks of miconazole administration.

within normal limits. Coccidioidal complement fixation titer was 4 plus at a dilution of 1:250.

Another course of amphotericin B therapy was started at 50 mg per day, but the patient's general condition deteriorated and several new coccidioidal abscesses developed that required multiple incisions and drainage. A painful new lesion appeared on the left shoulder and grew to 16 by 17 cm within a few days. The temperature spiked to 40.6°C (105°F) and leukocyte count was 24,000 (Figure 2). Hemoglobin decreased from 12.6 grams to 8 grams after four weeks of therapy. The patient became unable to leave his bed and severe weakness, weight loss, nausea, anorexia, emesis and headache were present.

On October 5, 1974, administration of amphotericin B was discontinued after a dose of 1.75 grams for this course and a cumulative dose of 4 grams had been given. After obtaining informed consent from the patient, 200 mg of miconazole,* diluted in 150 ml normal saline, was infused over a 30-minute period every eight hours by central venous catheter, since all peripheral veins had been thrombosed during amphotericin treatment. The patient's temperature returned to normal limits the day miconazole therapy was started and remained normal throughout the remainder of the hospital stay (Figure 2). The leukocyte count slowly returned to normal and the hemoglobin gradually increased without supplementary iron being given (Figure 2). Without incision and drainage, the large mass on the left shoulder subsided completely within 3½ weeks after treatment with miconazole was begun.

*Drug supplied by Janssen R&D, Inc., 501 George Street, New Brunswick, New Jersey.

The dose of miconazole was gradually increased to 400 mg every eight hours, then to 600 mg every eight hours without any notable side effects. When the dosage was increased to 800 mg every eight hours, the patient began to experience dryness of the eyes and mild pain in both knee joints. These symptoms completely disappeared after the dosage was reduced to 600 mg every eight hours. No more nausea, vomiting, anorexia or headache occurred—all of which were commonly encountered during the amphotericin B therapy. The patient gained both weight and strength. During miconazole therapy, skin and subcutaneous lesions healed and no new lesions appeared. After six weeks of miconazole therapy, it was noted on an x-ray study that the osteomyelitis of the right shoulder had healed and no new lesions appeared (Figure 3). The complement fixation titer remained 4 plus at 1:250 dilution. There were no untoward effects from the miconazole after a total of 68.4 grams over 59 days had been given.

Discussion

The mortality and morbidity from disseminated coccidioidomycosis in the black race with negative findings on skin tests are very high. Up to this time, except for amphotericin B, no other effective systemic antifungal agents have been available.

Miconazole nitrate, a substituted 1-phenethylimidazole with a molecular weight of 479.16, is synthetized by Janssen Pharmaceutica in Belgium and is a broad-spectrum antimycotic agent with antibacterial activity.[3] It inhibits the growth not only of most pathogenic fungi but also Gram-positive bacteria.[5] It has been available in Europe since 1971 and in the United States since April 1974, for topical use only. An intravenous preparation is available for investigational use only. Trials in Europe show the intravenous solution to be safe and effective in the treatment of systemic mycoses.[4-7] Since 1973, several cases of systemic candidiasis were treated with intravenous miconazole by Scheef and co-workers and Daneels and co-workers with good results.[6,7] One case of Candida albicans septicemia in a 51-year-old patient after renal transplantation was successfully treated with intravenously administered miconazole by Zazgornik and associates.[8] Hoeprich and Goldstein[9] recently reported their use of miconazole in a patient with coccidioidal meningitis who died of an unrelated complication

after 22 days of treatment. No side effects or systemic toxicity were observed from intravenous infusion of 1.2 grams per day for 30 days by European investigators.

The highest dosage used intravenously in Europe was 1.2 grams per day in divided doses. Due to the severe disseminated disease in this black patient, the intravenous dose was carried from 200 mg to 800 mg every eight hours. The dosage of 600 mg every eight hours was well tolerated. There were no immediate local or systemic side effects and no hematologic or biochemical abnormalities after a total of 68.4 grams of miconazole was given in 59 days. The serum concentration of the drug, after 400 mg intravenous miconazole, was 0.42 micrograms per ml after 2½ hours, and 0.22 micrograms per ml after 7½ hours, respectively. However, no attempt was made to use the serum level of miconazole as a guide for daily dosage administration. In our mycology laboratory, the minimal fungicidal concentration of miconazole *in vitro* was 0.218 micrograms per ml.

Despite its early investigational status and unknown potential for delayed side effects, the dramatic effectiveness of miconazole in a patient with coccidioidal osteomyelitis and disseminated abscesses and granulomata makes it worthy of further clinical trial.

Summary

A fulminating case of disseminated coccidioidomycosis in a black man was refractory to amphotericin B therapy, but successfully treated with miconazole. No immediate side effect or toxicity was observed with intravenous doses of up to 1.8 grams per day. The safety and effectiveness of this drug are worthy of further clinical study.

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Refer to: Garfinkle SE, Chiu GW, Cohen SE, et al: Spontaneous perforation of the neurogenic urinary bladder. West J Med 124:64-66, Jan 1976

Spontaneous Perforation of the Neurogenic Urinary Bladder

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ALTHOUGH SPONTANEOUS PERFORATION of the bladder has been reported in the literature,[1-4] little attention has been focused on its occurrence in patients with neurogenic bladder disturbances. Two cases of peritonitis due to spontaneous intraperitoneal perforation of the urinary bladder in neurologically handicapped patients were recently seen on the general surgical service at the University of California, Davis, Sacramento Medical Center.

Reports of Cases

CASE 1. A 21-year-old man sustained a fracture dislocation of the fourth and fifth cervical vertebrae in an automobile accident. The injury resulted in a spastic paralysis below the level of the sixth cervical vertebra. While the patient was in hospital, urinary drainage was instituted with an indwelling urethral catheter. Two years later the patient was readmitted for treatment of sacral decubiti and multiple bladder calculi. Cystogram disclosed a "Christmas tree" appearance of the bladder and bilateral ureteral reflux. Intravenous pyelogram showed small radiopaque calculi in the right renal pelvis. Results of cystometric examination were consistent with a spastic neurogenic bladder. A cystolithalopaxy was done. Postoperatively, the indwelling catheter was removed and

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