

Letters

RAPID DESENSITIZATION TO FLUCONAZOLE (DIFLUCAN)

Fluconazole (Diflucan) is a triazole antifungal medication administered as a suspension or a tablet or delivered intravenously. It is effective for fungal infections of the nails, oral and vaginal mucosal and generalized candidiasis, cryptococcal meningitis, and prophylaxis of cryptococcal infections in immunocompromised individuals. Adverse effects include hepatitis, leucopenia, thrombocytopenia, gastrointestinal distress, headache, anaphylaxis, and rashes.¹⁻⁸ These rashes include conditions ranging from self-limited to life threatening, including Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, fixed drug eruption anaphylactoid purpura, maculopapular eruption, and acute generalized exanthematous pustulosis.¹⁻⁹ The incidence of adverse effects is increased in human immunodeficiency virus-infected individuals.^{1,9,10}

Fluconazole desensitization has been described in the literature but only with a several-day schedule.^{1,10} We describe a rapid "desensitization" with fluconazole performed on 6 occasions in 3 to 4 hours in an office for a presumed immunologic reaction.

A 63-year-old white woman, a retired teacher with severe asthma, maintained a forced expiratory volume in 1 second of 95% to 84%, a forced vital capacity of 96%, and a forced expiratory flow between 25% and 75% of 92% consistently since 1999 while taking fluticasone propionate (Advair) 500/50, 1 puff twice daily, and montelukast sodium (Singulair), 10 mg once daily at bedtime, with oral steroids every other month. She developed recurrent oral candidiasis. Her candi-

diasis was unresponsive to nystatin and clotrimazole (Mycelex) and required fluconazole for resolution. Per pharmacy records, she was treated with fluconazole for 14-day courses beginning in February 2002 and subsequently in March, June, and August 2003 without event. However, she developed hives on the chest on 2 occasions during treatment with fluconazole, noted in April 2004. Her first reaction developed 2 days into fluconazole therapy. Her second reaction involved oropharyngeal and lower airway symptoms requiring diphenhydramine and albuterol metered-dose inhaler therapy. She had a medical history of documented penicillin and sulfa sensitivity by skin test.

She was empirically desensitized for subsequent episodes of candidiasis in April, July, September, and December 2004 and April and September 2007 for presumed IgE-mediated reaction because fluconazole was the only medication efficacious for her condition. Desensitization was accomplished using a methylcellulose solution (Oraplus; Paddock Labs, Minneapolis, Minnesota) of 100 mL to dissolve a 200-mg tablet of fluconazole, 2 mg/mL, then diluting to 1/10,000 with methylcellulose solution (Table 1). In May 2007, intradermal skin testing at 1/1,000 (0.2 mg) was performed using a 200-mg tablet dissolved in 100 mL of methylcellulose solution (Oraplus) (2-mg/mL fluconazole), then diluted 1/10 to a final concentration of 1/1,000 (0.2 mg/mL). The intradermal skin test result was positive (5-mm wheal/10-mm flare) at the 1/1,000 concentration (0.2 mg/mL) with histamine reaction (10-mm wheal/20-mm flare). The intradermal skin test result to fluconazole was negative in an unaffected volunteer (C.R.). An IgE-mediated reaction was presumed with a positive skin test result and a history of urticarial reaction.

Disclosures: Authors have nothing to disclose.

Table 1. Desensitization Procedure^a

Step	Concentration, mg/mL	Volume administered, mL	Dose administered, mg	Cumulative dose, mg
1	0.02	1	0.02	0.02
2	0.02	2	0.04	0.06
3	0.02	4	0.08	0.14
4	0.2	0.8	0.16	0.30
5	0.2	1.6	0.32	0.62
6	0.2	3.2	0.64	1.26
7	2	0.75	1.50	2.76
8	2	1.5	3.00	5.76
9	2	3	6.0	11.76
10	20	0.6	12	23.76
11	20	1.2	24	47.76
12	20	2.5	50	97.76
13	20	5.0	100	197.76

^aThe procedure is given for rapid desensitization of fluconazole, 0.02 mg/mL. There was a 15-minute interval between doses. The patient was observed for 2 hours without event.

Desensitization was approached using a standard protocol beginning at 1/10,000 (0.02 mg) or 1/10 of the bioassay skin test concentration (1/1,000) of the expected dose (200 mg) and doubling every 15 minutes until approximately 200 mg was administered. After oral desensitization to an approximately 197-mg total dose (Table 1), 200 mg/d was then administered for 14 days, beginning the following day. In July 2004, she developed transient hives 2 hours after desensitization, which resolved with antihistamine within the week. In April 2007, with her fifth desensitization, she developed disseminated, flat, 2- to 7-cm circular lesions in the right frontal and right precordial areas beginning 4 hours after desensitization. These lesions progressed to a macular rash that was pruritic beginning 4 hours after desensitization and generalizing by 48 hours. There was a single blistered lesion in her right frontal and axillary area. She was treated with prednisone, beginning at 60 mg and tapered 10 mg/d, and diphenhydramine, 25 mg every 4 hours, with resolution of her rash within the week. She completed 2 weeks of fluconazole therapy as prescribed. In September 2007, she was taking prednisone, 10 mg/d, for an asthma exacerbation at desensitization but discontinued prednisone therapy. A transient exanthem developed that was diffuse and maculopapular, involving the upper torso and extremities only, with an isolated blistered vesicle beginning 4 hours after desensitization. The vesicle resolved within 3 days after completing 48 hours of prednisone therapy, 60 mg/d.

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REMISSION OF SCHNITZLER SYNDROME AFTER TREATMENT WITH ANAKINRA

Schnitzler syndrome is a rare and underrecognized disorder characterized by chronic urticarial rash, IgM (or rarely IgG) monoclonal gammopathy, and at least 2 of the following: recurrent fevers, arthralgia, bone pain, lymphadenopathy, hepatosplenomegaly, elevated inflammatory markers, leukocytosis, and abnormal bone morphology.¹ Because the clinical signs associated with Schnitzler syndrome are varied, patients are often evaluated by multiple specialists before a diagnosis is made. Correct diagnosis of Schnitzler syndrome is essential because approximately 15% of patients will develop lymphoproliferative disease, and, therefore, long-term follow-up is important.¹

No approach has been consistently effective in treating the urticarial rash associated with Schnitzler syndrome. H₁/H₂ blockers, inhibitors of neutrophil migration (dapson, colchicine), plasmapheresis, and intravenous immunoglobulin have not been effective.¹ A few case reports^{1–3} have suggested improvement with high-dose corticosteroids, thalidomide, and quinolones, but these treatments are not universally effective, and widespread clinical use is limited by their associated adverse effects.

We describe a 72-year-old man who was evaluated for a 2-year history of diffuse urticaria. The rash consisted of moderately pruritic, rose-colored, mildly edematous oval lesions that occurred daily and typically resolved without residual skin changes after 24 to 48 hours (Fig 1). Skin biopsy revealed a perivascular infiltrate of predominantly mononuclear cells. The patient never experienced angioedema. During the ensuing year, he developed a nonproductive cough, daily low-grade fevers, intermittent night sweats, bone pain, a 10-lb weight loss, and palpable inguinal and axillary lymph nodes. He also complained of breast tenderness and swelling. Laboratory studies showed a moderately elevated erythrocyte sedimentation rate of 32 mm/h and a C-reactive protein level of 8.3 mg/L. Blood cell count revealed leukocytosis (22,200/mm³ with 89% neutrophils), anemia (hemoglobin level, 10.4 g/dL), and thrombocytosis (522 k/mm³). Results of complement and thyroid studies were normal. Luteinizing hormone, follicle-stimulating hormone, and prolactin levels were normal. Serum immunoglobulins showed mildly elevated IgG (1,760 mg/dL) and IgM (304 mg/dL) levels and a normal IgA level (127 mg/dL). Serum protein electrophoresis demonstrated a monoclonal IgM protein with κ light chains on immunofixation. No Bence-Jones proteinuria was evident. A chest computed tomograph demonstrated bilateral axillary lymphadenopathy and gynecomastia, and an abdominal/pelvic computed tomograph showed bilateral enlarged inguinal nodes. Results of purified protein derivative of tuberculin testing were negative. An inguinal lymph node biopsy revealed reactive follicular and interfollicular lymphoid hyperplasia, and a bone marrow biopsy specimen demonstrated

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