

These results are very similar to the MID (approximately 0.5) determined for other disease-specific quality of life questionnaires that use 7-point response options (e.g., asthma, pediatric asthma, chronic respiratory disease, heart failure). Although we only tested the RQLQ in this study, the results are probably applicable to the Rhinitis Quality of Life Questionnaire,⁴ which is almost identical to the original instrument except that all references to eye symptoms have been removed. In addition, they should be applicable to the Adolescent Rhinoconjunctivitis Quality of Life Questionnaire,⁵ which is also very similar to the adult version, except that there is no sleep domain and there are additional questions concerning ability to concentrate.

Desensitization for fluconazole hypersensitivity

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The use of fluconazole continues to increase with present indications including fungal infections of the nails, skin, oral and vaginal mucosa, systemic candidiasis, and cryptococcal meningitis. Fluconazole is well tolerated with few adverse effects. The main toxicities include hepatitis, leukopenia, thrombocytopenia, gastrointestinal distress, headache, anaphylaxis, and rash.¹⁻⁴ Rashes have included: Stevens-Johnson syndrome, diffuse erythema, angioedema, maculopapular and fixed drug eruptions. Herein we present a case of hypersensitivity to fluconazole that first manifested as a rash. Because of the need to reinstitute fluconazole, we elected to test dose and desensitize the patient. This is apparently the first description of such a procedure with fluconazole.

CASE REPORT

T.P., a 36-year-old man, was referred because of a rash caused by fluconazole. His medical history was positive for HIV. His last T-4 lymphocyte count was

REFERENCES

1. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;21:77-83.
2. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life instrument. *J Clin Epidemiol* 1994;47:81-7.
3. Juniper EF, Ferrie PJ, Guyatt GH, Griffith LE. Primary treatment for seasonal allergic rhinitis: an inhaled nasal steroid (fluticasone) or a non-sedating antihistamine (terfenadine)? A management study. *Can Med Assoc J*. Submitted.
4. Juniper EF, Guyatt GH, Andersson B, Ferrie PJ. Comparison of powder and aerosolized budesonide in perennial rhinitis: validation of rhinitis quality of life questionnaire. *Ann Allergy* 1993;70:225-30.
5. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. *J Allergy Clin Immunol* 1994;93:413-23.

below 50. His course was complicated with cryptococcal meningitis, *Pneumocystis pneumonia*, sinusitis, and drug allergies. Cryptococcal meningitis was initially treated with amphotericin B. After 3 weeks of therapy, the patient was switched to oral fluconazole therapy, 400 mg a day. On day 4 of therapy a pruritic rash in both axilla and hypereosinophilia developed. After 1 month, the dose was decreased to 200 mg a day, but his symptoms progressed and included hives, dyspnea, and tachycardia. During this time interval he was noted to have one oral ulceration. Within a few days after discontinuing fluconazole, his symptoms resolved.

He was switched to itraconazole as secondary prophylaxis. After 6 months, cryptococcal meningitis developed. Amphotericin was restarted with good response. After completion of 3 weeks of intravenous amphotericin, the patient was referred for evaluation to determine whether fluconazole could be restarted. Because of the lack of an acceptable protocol for skin testing, we elected to test dose the patient. We chose a prolonged test dosing protocol, starting at less than one one thousandth of the dose and gradually increasing the dose by doubling it each day. This procedure was complicated by a transient macular, papular, pruritic rash on the upper trunk and under the axilla area from days 4 to 6, which resolved despite increasing the dose. Signs of anaphylaxis did not develop, and mucus membranes remained normal. Within 15 days the patient was receiving full prophylactic doses of 400 mg of fluconazole orally each day. He has been receiving therapy for over

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TABLE I. Procedure for fluconazole desensitization

Day	Concentration	Dose	Total mg
1	1 mg/ml	0.2 ml	0.2
2	1 mg/ml	0.4 ml	0.4
3	1 mg/ml	0.8 ml	0.8
4	1 mg/ml	1.6 ml	1.6
5	1 mg/ml	3.2 ml	3.2
6	1 mg/ml	6.4 ml	6.4
7	10 mg/ml	1.0 ml	10
8	10 mg/ml	2.0 ml	20
9	10 mg/ml	4.0 ml	40
10	50 mg tablet	1	50
11	50 mg tablet	2	100
12	50 mg tablet	3	150
13	200 mg tablet	1	200
14	100 mg tablet	3	300
15	200 mg tablet	2	400

Continue 400 mg each day without stopping.
All doses were given orally.

4 months without a return of symptoms. The protocol used is outlined in Table I.

DISCUSSION

Fluconazole has advantages over amphotericin B. It can be given orally and has a more benign adverse effect profile. The major dose-limiting toxic effect of amphotericin B is renal failure. Though renal toxicity is reduced by restricting doses and elongating the interval between doses, the need for intravenous dosing makes it a less than optimal drug for long-term prophylaxis. Fluconazole can be given orally once per day, making compliance easy. Of the azoles, fluconazole has the most data supporting its effectiveness in *Cryptococcus meningitis*. Itraconazole does not appear to be as effective. Itraconazole use is further compromised in advanced HIV disease because of the high frequency of achlorhydria in this population. An acid environment is necessary for absorption of itraconazole but not for absorption of fluconazole.

The most common adverse effects of fluconazole are gastrointestinal symptoms and elevated liver function test values. Most patients with elevated liver function test values remain free of symptoms; however, fatal hepatitis has been documented.⁵

Other adverse effects include: leukopenia, thrombocytopenia, headaches, Stevens-Johnson syndrome, angioedema, fixed drug reactions, and maculopapular rashes.¹⁻⁴ The type of hypersensitivity underlying the rash induced by fluconazole has not been determined. The role of skin testing with fluconazole to determine whether the mechanism is an IgE-mediated reaction is also unknown.

In this report we describe a patient who required fluconazole therapy, despite the risk, for the reasons outlined in the case report. We elected to desensitize the patient by means of a protocol for trimethoprim/sulfamethoxazole described by Absar et al.⁶ Their protocol outlined a 10-day desensitization program, differing little from the 15-day procedure we used. Of the 28 patients who started the study by Absar et al.,⁶ 23 tolerated the procedure and continued taking trimethoprim/sulfamethoxazole. Before this report, desensitization to trimethoprim/sulfamethoxazole or other medications was performed in only a small number of patients with HIV by means of various protocols. The limited experience with hypersensitivity to fluconazole in patients with HIV makes it difficult to make any recommendations; however, it does appear that the procedure we used was safe and effective. It should be noted that cytopenias and exfoliative rashes are contraindications for desensitization or rechallenge with fluconazole.

REFERENCES

1. Neuhaus G, Pavic N, Pletscher M. Anaphylactic reaction after oral fluconazole. *BMJ* 1991;302:1341.
2. Gussenhoven MJE, Haak A, Peereboom-Wynia JDR. Stevens-Johnson syndrome after fluconazole. *Lancet* 1991;338:120.
3. Abbot M, Hughes DL, Patel R, Kinghorn GR. Angioedema after fluconazole. *Lancet* 1991;338:633.
4. Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch G, Feldman AR, Meyers JD, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation: a prospective, randomized, double-blind study. *J Infect Dis* 1995;171:1545-52.
5. Munoz P, Moreno S, Berenguer J, Bernaldo de Quiros, Bouza E. Fluconazole related hepatotoxicity in patients with acquired immunodeficiency syndrome. *Arch Intern Med* 1991;151:1020-1.
6. Absar N, Daneshvar H, Beall G. Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients. *J Allergy Clin Immunol* 1994;93:1001-5.