Topical Management of Superficial Fungal Infections: Focus on Sertaconazole

James Q. Del Rosso, DO; Joseph Bikowski, MD

Sertaconazole, a topical azole antifungal agent, exhibits a dual antifungal mechanism of action, antibacterial activity, and anti-inflammatory properties and demonstrates a broad spectrum of activity against numerous fungal pathogens. Topical sertaconazole is efficacious and safe in the treatment of cutaneous dermatophytosis, tinea versicolor (pityriasis versicolor), cutaneous candidiasis, mucosal candidiasis, intertrigo, and seborrheic dermatitis. Pharmacokinetic properties demonstrate an epidermal reservoir effect posttreatment. Sertaconazole has proven to be both safe and well tolerated, based on available data worldwide.

Superficial fungal infections are commonly encountered in office-based dermatologic practice, are estimated to affect up to 20% of individuals living in the United States, and are most commonly caused by dermatophytes and yeasts.[1-5] The dermatophyte organisms are predominantly from the *Trichophyton* species, including *Trichophyton rubrum*, *Trichophyton mentagrophytes,* and *Trichophyton tonsurans*, the latter being the most common cause of tinea capitis in the United States.[1,2,4,5] Tinea pedis, primarily the interdigital and dry plantar types, is caused most often by *T rubrum* and *T mentagrophytes* and is the most commonly encountered dermatophyte infection in the United States.[1,2,4,6] *Trichophyton verrucosum*, *Microsporum canis*, *Microsporum gypseum*, and *Epidermophyton floccosum* are sometimes determined to be causative organisms of cutaneous dermatophyte infections.[4] *M canis*, a zoophilic organism, may be a cause of cutaneous dermatophytosis in adults and children, or of tinea capitis primarily in children, when there is exposure to an infected animal, usually a cat.[7,8]

The most common yeasts involved in causing superficial mycotic infections in the United States are *Candida albicans*, associated with several cutaneous and mucosal presentations of candidiasis, such as vulvovaginitis, oral thrush, perlèche, intertrigo, and paronychia, and *Malassezia furfur*, the causative organism of tinea versicolor.[3,4,9,10]

Important Clinical Considerations

Clinical diagnosis, although accurate in many cases, may be difficult as many skin and mucosal disorders may simulate superficial fungal infections.[2-8,10-16] Diagnostic testing, such as potassium hydroxide preparation and fungal culture, is very helpful in ensuring an accurate diagnosis.

Tinea capitis is seen primarily in children, although adults, including elderly patients, may be affected on occasion.[7,8,11-13] A high index of suspicion is needed when diagnosing tinea capitis in an adult patient.[12,13] Importantly, as the most common cause of tinea capitis in the United States, *Trichophyton tonsurans* produces an endothrix pattern of hair shaft invasion; the infected hairs do not fluoresce on exposure to a Wood light, thus rendering this diagnostic tool unhelpful when fluorescence is not observed.[17]

Dry plantar tinea pedis, seen primarily in adults and caused almost exclusively by *T rubrum*, is frequently associated with toenail dermatophyte onychomycosis, and in some cases with concomitant diffuse dermatophytosis, including tinea cruris, tinea corporis, tinea manus, fingernail dermatophyte onychomycosis, or a combination of these conditions.[1,2,6,14] In such patients, there is often an underlying genetic trait that creates an "immunologic blind spot" against *T rubrum*, thus rendering the affected individual more susceptible to carriage, primary infection,

Dr. Del Rosso is Clinical Associate Professor, Dermatology, University of Nevada School of Medicine, Las Vegas; Clinical Associate Professor, Dermatology, Touro University College of Osteopathic Medicine, Las Vegas; and Dermatology Residency Director, Valley Hospital Medical Center, Las Vegas. Dr. Bikowski is Clinical Associate Professor, Dermatology, Ohio State University, Columbus, and Director, Bikowski Skin Care Center, Sewickley, Pennsylvania.

Dr. Del Rosso is a consultant, researcher, and speaker for Medicis Pharmaceutical Corporation, OrthoNeutrogena, and Stiefel Laboratories, Inc. Dr. Bikowski is a consultant and speaker for OrthoNeutrogena.

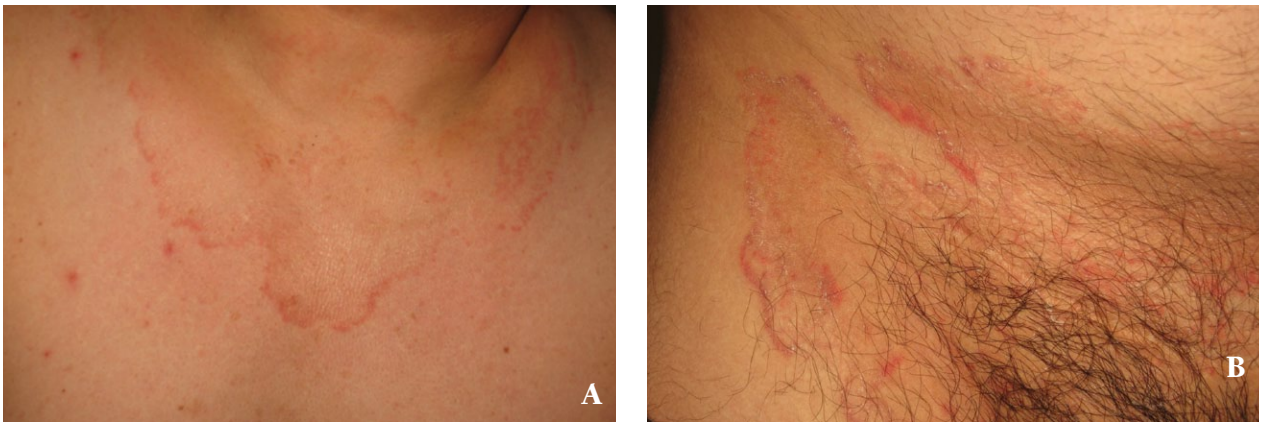

Figure 1. Extensive tinea corporis (A) and tinea cruris (B) in an adult male patient.

and reinfection by this organism at multiple cutaneous sites, especially the feet and toenails.[6,14] Figures 1A and 1B demonstrate extensive tinea corporis and tinea cruris in an adult male patient who presented with concomitant dry plantar tinea pedis and toenail onychomycosis caused by *T rubrum*. Although tinea pedis and onychomycosis are uncommon in people younger than 16 years, affected pediatric patients are usually found in families who exhibit this genetic predisposition.[6,14,15,18]

Development of tinea versicolor is uncommon before onset of puberty and is frequently recurrent since the inciting organism is part of the normal cutaneous microflora. Although the cause of individual susceptibility is not clear, some people are prone to recurrence, characterized by a change from the commensal spore stage of the yeast to the pathogenic hyphal phase (*M furfur*).[10]

Cutaneous and mucosal candidiasis, frequently caused by *C albicans* but sometimes by other *Candida* species (*Candida glabrata, Candida tropicalis*, *Candida krusei*), develops when there is opportunity for colonization and proliferation of the yeast organisms.[3] Contributing factors may include local changes promoting overgrowth of the yeast, such as intertriginous moisture and friction, and systemic factors, such as antibiotic selection pressure, immunosuppression, or poor control of diabetes.[3]

Tinea incognito occurs when a topical corticosteroid is applied to a dermatophyte infection.[18,19] As the corticosteroid blunts the immunologic response directed against the dermatophyte organism, the fungi further proliferate unopposed, leading to visible accentuation of the eruption. Additionally, the anti-inflammatory activity of the corticosteroid alters the visible appearance of the eruption, thus confounding the ability to make an accurate clinical diagnosis. In some cases, tinea profunda (Majocchi granuloma) may develop, rendering the eruption less likely to be responsive to topical antifungal therapy alone. Figure 2 depicts a patient with facial tinea incognito that developed after application of a midpotency topical corticosteroid. The eruption was diagnosed based on a high index of suspicion as well as potassium hydroxide preparation, which demonstrated multiple long, branched hyphae, and was effectively treated with twice-daily application of sertaconazole nitrate 2% cream used over a 4-week period. In most cases, eradication of tinea profunda requires use of an oral antifungal agent that is active against dermatophyte organisms.

Certain superficial fungal infections, such as tinea capitis, onychomycosis (other than white superficial onychomycosis), and tinea profunda, are not typically responsive to topical antifungal therapy alone and require use of oral antifungal therapy.[20-22] In some cases, tinea incognito and other superficial dermatophyte and yeast infections may require use of an oral antifungal agent to clear the infection.[20-22] Therefore, the judgment of the clinician based on factors related to the clinical presentation and medical

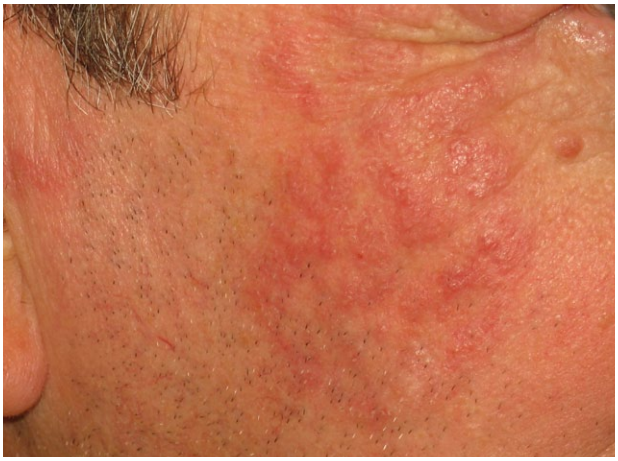

Figure 2. Facial tinea incognito that developed after application of a midpotency topical corticosteroid.

Spectrum of Clinical Activity of Topical Antifungal Agents*[23]

Generic	OTC	Superficial Dermatophytes	*Candida*	*Pityrosporum* (*Malassezia furfur*)
Butenafine†	−	+	+	+‡
Ciclopirox§	−	+	+	+
Clotrimazole‖	+	+	+	+
Econazole‖	−	+	+	+
Ketoconazole	−	+	+	+
Naftifine¶	−	+	+	+‡
Nystatin**	−	−	+	−
Oxiconazole‖	−	+	−	−
Sertaconazole‖	−	+	+	+
Sulconazole‖	−	+	+	+
Terbinafine¶	+	+	+‡	+‡

*OTC indicates over the counter; −, no clinical activity; +, clinical activity.
†Benzylamine.
‡Clinical efficacy limited or uncertain.
§Hydroxypyridine.
‖Azole.
¶Allylamine.
**Polyene.

history of the individual patient and follow-up to ensure that treatment has been effective are vital components in the management of these disorders.

Available Topical Antifungal Agents

Several topical antifungal agents are available for treatment of superficial fungal infections. These agents may differ in their mechanisms of actions, spectrum of activity, available formulations, indications, and recommended frequency of use. The Table summarizes several available topical antifungal agents, including spectrum of activity for clinical use and structural class designations.[23]

There are several options available to clinicians for treatment of superficial dermatophyte and yeast infections. Nystatin is a topical polyene antifungal agent that exhibits activity against superficial cutaneous and mucosal infections caused by *C albicans* but is not useful for treatment of dermatophyte infections or tinea versicolor.[20,21,23,24] Azole antifungal agents, such as ketoconazole, econazole, sertaconazole, oxiconazole, and sulconazole, exhibit a broad spectrum of activity and have demonstrated efficacy in the treatment of cutaneous dermatophyte infections, candidiasis, and tinea versicolor.[20,21,23,24] The topical allylamines, terbinafine and naftifine, and the benzylamine agent butenafine exhibit broad-spectrum antifungal activity in vitro and are used most commonly for treatment of cutaneous dermatophyte infections, with efficacy also reported for cutaneous candidiasis and tinea versicolor.[20,21,23,24] Butenafine has been reported to be more active than naftifine and terbinafine against *C albicans*.[20,25] Ciclopirox is a hydroxypyridine antifungal agent effective in the treatment of cutaneous dermatophyte infections, candidiasis, and tinea versicolor.[20,21,23,24]

Sertaconazole

Sertaconazole nitrate 2% cream is the most recently introduced topical azole antifungal agent in the United States indicated for treatment of tinea pedis.[24] Additionally, sertaconazole is marketed in more than 20 countries worldwide in a variety of formulations, including cream, powder, gel, and solution for cutaneous fungal infections, and intravaginal tablet and cream for vulvovaginal candidiasis.[24,26]

Mechanisms of Action

Similar to other azole antifungal agents, sertaconazole inhibits lanosterol 14-alpha-demethylase, resulting in

subsequent reduction in synthesis of ergosterol, the primary sterol contributing to fungal cell membrane function and stability.[20,24] The decreased availability of ergosterol coupled with intracellular accumulation of 14-alpha-methylsterols leads to increased membrane rigidity, alterations in membrane permeability, changes in important membrane-bound enzymes, growth inhibition, and, ultimately, death of the fungal cell.[20,24] In addition, it has been reported that sertaconazole induces direct damage to membranes of susceptible organisms through binding to nonsterol lipids, resulting in impaired membrane regulatory function; leakage of intracellular contents, such as adenosine triphosphate; and rapid cell death.[24,27] Sertaconazole has also been shown to exhibit anti-inflammatory activity and antibacterial activity against some staphylococci and streptococci.[24,27-32]

Anti-inflammatory Properties

The anti-inflammatory properties of several antifungal agents, including miconazole, fluconazole, sertaconazole, terconazole, ketoconazole, and ciclopirox, were studied in multiple in vivo and in vitro preclinical models of cutaneous inflammation and pruritus, with sertaconazole exhibiting the greatest ability to suppress cytokine release from phytohemagglutinin-stimulated human peripheral blood lymphocytes.[29] It has also been reported that sertaconazole was superior to other tested azole antifungal agents, including ketoconazole, in reducing irritant dermatitis in an ear edema model and that it reduced scratching response in a murine model of pruritus comparable to hydrocortisone.[27] The anti-inflammatory properties of an antifungal agent, such as sertaconazole, are believed to be important in symptom reduction, especially early in the course of treatment, and may obviate the need for application of other topical antipruritic agents.

Pharmacokinetic Properties

The lipophilicity of sertaconazole, related to its synthesis with a lipophilic benzothiophene ether, is believed to contribute to enhancement of epidermal penetration after topical application, with negligible systemic absorption noted on plasma analysis.[24,27,33] A cutaneous reservoir effect has been noted, with 72% of the applied dose of sertaconazole present at 24 hours after application and with a cutaneous retention time test demonstrating the superior antifungal effect of sertaconazole at 12, 24, and 48 hours after application as compared with that of bifonazole.[27,33] Although approved product labeling for sertaconazole nitrate 2% cream in the United States indicates an application frequency of twice daily, the persistence of antifungal activity after application and the cutaneous reservoir effect explain why this agent has been shown to be effective after application once daily.[27]

Spectrum of Activity

Sertaconazole has been shown to be active against dermatophytes, including *T rubrum, T mentagrophytes,* and *E floccosum;* yeasts, including *C albicans, C glabrata, C krusei, Candida parapsilosis, C tropicalis,* and *M furfur;* and some gram-positive bacteria, including staphylococcal and streptococcal organisms.[24,27,30-32,34] The antifungal activity of sertaconazole against several fungal isolates known to cause superficial fungal infections has been shown to be comparable or superior to that of other topical antifungal agents, including bifonazole and terbinafine.[24,27,31,32] Antifungal resistance to sertaconazole has not been demonstrated.[27,31,32]

Clinical Applications

Tinea Pedis

In 2 randomized, multicenter, double-blind, parallel-group, vehicle-controlled trials (N=349), patients with interdigital tinea pedis were treated with either sertaconazole nitrate 2% cream or vehicle cream twice daily for 4 weeks.[35] Overall treatment success, based on investigator global assessment of signs and symptoms, demonstrated statistical superiority ($P<.0009$) of sertaconazole (57.9%) versus vehicle (39.9%). Relief of pruritus was reported to be rapid by patients in the sertaconazole arm, with 77% indicating mild or absent pruritus within 7 days as compared with 20% at baseline. After 3 weeks of application, 64% of sertaconazole-treated patients reported no pruritus as compared with 44% of patients treated with vehicle cream ($P=.0001$). Additionally, a mycologic cure rate of 66.2% was sustained at 6 weeks (2 weeks posttreatment) in sertaconazole-treated patients, a rate 3-fold higher than that observed in the vehicle arm of the trial ($P<.0001$). Tolerability and safety were favorable in both study arms, with cutaneous adverse reactions comparable in actively treated and vehicle-treated patients. Figures 3A and 3B demonstrate clinical clearance of tinea pedis after 2 weeks of use of sertaconazole nitrate 2% cream applied twice daily.

Other Reported Uses

The efficacy, safety, and tolerability of sertaconazole 2% cream (n=295) and miconazole nitrate 2% cream (n=274) applied twice daily for 28 days were evaluated in several presentations of cutaneous mycoses, including tinea pedis, tinea corporis, tinea barbae, tinea manus, and tinea cruris.[27] Treatment with sertaconazole demonstrated a definite trend toward greater efficacy

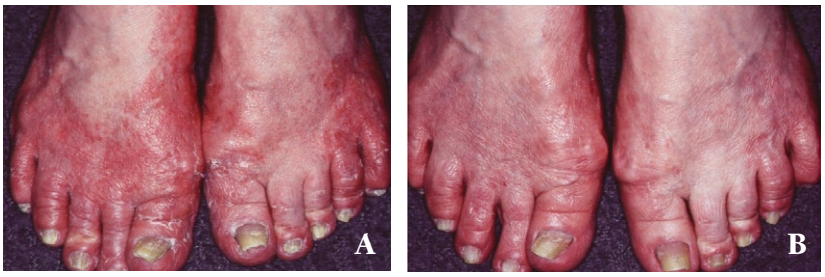

Figure 3. Tinea pedis before (A) and after (B) 2 weeks of treatment with sertaconazole nitrate 2% cream applied twice daily.

and more rapid clinical clearance. At the third follow-up visit, microscopic examination was negative in 86.8% and 79.2% of patients treated with sertaconazole and miconazole, respectively ($P<.02$). None of the patients in the sertaconazole-treated group and 5 patients in the miconazole-treated group developed contact dermatitis at application sites.

Topical sertaconazole has also been shown to be effective for tinea versicolor and seborrheic dermatitis.[27] Although seborrheic dermatitis is an inflammatory dermatosis and not a fungal infection, overgrowth of *M furfur* appears to be a component of its pathogenesis.

Twice-daily application of sertaconazole 2% cream for up to 4 weeks is effective in eradicating tinea versicolor.[27] In European trials, a 2% gel formulation of sertaconazole applied once every 3 days over a 4-week period was effective for the treatment of seborrheic dermatitis and proved to be superior to ketoconazole 2% gel.[26,27]

In one report, patients with intertrigo of the toe webs, groin, umbilicus, and axillae were successfully treated with sertaconazole nitrate 2% cream (N=10).[36]

Sertaconazole vaginal tablet and cream formulations, approved for use in several countries other than the United States, have been studied extensively as treatments for vulvovaginitis and have demonstrated both efficacy and safety.[26]

Safety of Topical Sertaconazole

Similar to other topical azole antifungal agents, sertaconazole exhibits a favorable tolerability and safety profile and has not been associated with any serious adverse events.[24,26,27,35] Allergic contact dermatitis, including cross-sensitivity with other azole antifungal agents, is rare.[37]

Comment

Sertaconazole, a topical azole antifungal agent, exhibits a dual antifungal mechanism of action, antibacterial activity, and anti-inflammatory properties and demonstrates a broad spectrum of activity against numerous fungal pathogens. Multiple studies have demonstrated efficacy and safety in the treatment of cutaneous dermatophytosis, tinea versicolor, cutaneous candidiasis, mucosal candidiasis, intertrigo, and seborrheic dermatitis. Pharmacokinetic properties demonstrate an epidermal reservoir effect posttreatment, which may allow for once-daily application and may also be applicable for maintenance treatment in patients predisposed to reinfection. Based on data collected from studies and clinical experience worldwide, topical sertaconazole is both safe and well tolerated.

References

1. Weitzman I, Summerbell RC. The dermatophytes. *Clin Microbiol Rev*. 1995;8:240-259.
2. Tschen EH. Clinical aspects of superficial fungal infections. *Dermatol Clin*. 1984;2:3-17.
3. Jorizzo JL. The spectrum of mucosal and cutaneous candidiasis. *Dermatol Clin*. 1984;2:19-27.
4. Drake LA, Dinehart SM, Farmer ER, et al; Guidelines/Outcomes Committee; American Academy of Dermatology. Guidelines of care for superficial mycotic infections of the skin: tinea corporis, tinea cruris, tinea faciei, tinea manuum, and tinea pedis. *J Am Acad Dermatol*. 1996;34:282-286.
5. Guidelines/Outcome Committee; American Academy of Dermatology. Guidelines of care for superficial mycotic infections of the skin: mucocutaneous candidiasis. *J Am Acad Dermatol*. 1996;34:110-115.
6. Leyden JJ, Aly R. Tinea pedis. *Semin Dermatol*. 1993;12:280-284.
7. Frieden IJ. Tinea capitis. In: Aly R, Beutner KR, Maibach H, eds. *Cutaneous Infection and Therapy*. New York, NY: Marcel Dekker; 1997:169-181.
8. Tinea capitis: current concepts. *Pediatr Dermatol*. 1985;2:224-237.
9. Faergemann J. *Pityrosporum* infections. In: Elewski BE, ed. *Cutaneous Fungal Infections*. New York, NY: Igaku-Shoin; 1992:69-83.
10. Hebert A. Tinea versicolor. *Dermatol Clin*. 1984;2:21-43.
11. Raimer SS, Petrusick TW. Superficial fungal infections in children. *Dermatol Clin*. 1984;2:57-65.
12. Moberg S. Tinea capitis in the elderly: a report on two cases caused by *Trichophyton tonsurans*. *Dermatologica*. 1984;169:36-40.
13. Conerly SL, Greer DL. Tinea capitis in adults over fifty years of age. *Cutis*. 1988;41:251-252.
14. Aly R. Tinea pedis: epidemiology, clinical manifestations, pathophysiology, and therapy. In: Aly R, Beutner KR, Maibach H, eds. *Cutaneous Infection and Therapy*. New York, NY: Marcel Dekker; 1997:139-148.
15. Gupta AK, Sibbald RG, Lynde CW, et al. Onychomycosis in children: prevalence and treatment strategies. *J Am Acad Dermatol*. 1997;36:395-402.
16. Habif TP. Topical therapy and topical corticosteroids. In: Habif TP, ed. Clinical Dermatology. 4th ed. Edinburgh, UK: Mosby; 2004: chapter 2.
17. Prevost E. The rise and fall of fluorescent tinea capitis. *Pediatr Dermatol*. 1983;1:127-133.

18. Rashid A, Richardson MD. Pathogenesis of dermatophytosis. In: Aly R, Beutner KR, Maibach H, eds. *Cutaneous Infection and Therapy*. New York, NY: Marcel Dekker; 1997:127-137.
19. Alston SJ, Cohen BA, Braun M. Persistent and recurrent tinea corporis in children treated with combination antifungal/corticosteroid agents. *Pediatrics*. 2003;111:201-203.
20. Zhang AY, Camp WL, Elewski BE. Advances in topical and systemic antifungals. *Dermatol Clin*. 2007;25:165-183.
21. Gupta AK, Sauder DN, Shear NH. Antifungal agents: an overview. part I. *J Am Acad Dermatol*. 1994;30:677-698.
22. Gupta AK, Sauder DN, Shear NH. Antifungal agents: an overview. part II. *J Am Acad Dermatol*. 1994;30:911-933.
23. Del Rosso JQ. Differentiation of topical antifungal agents used for treatment of superficial mycotic infections based on scientific evidence. Poster presented at: Summer Meeting of the American Academy of Dermatology; August 1-5, 2007; New York, NY.
24. Phillips RM, Rosen T. Topical antifungal agents. In: Wolverton SE, ed. *Comprehensive Dermatologic Drug Therapy*. 2nd ed. Philadelphia, Pa: Saunders Elsevier; 2007:chapter 29.
25. Syed TA, Maibach HI. Butenafine hydrochloride: for the treatment of interdigital tinea pedis. *Expert Opin Pharmacother*. 2000;1:467-473.
26. Torres J, Marquez M, Camps F. Sertaconazole in the treatment of mycoses: from dermatology to gynecology. *Int J Gynecol Obstet*. 2000;71(suppl 1):S3-S20.
27. Del Rosso JQ. Topical azole antimycotics for superficial fungal infections. *Clin Update Skin Allergy News*. 2007:38(suppl):1-4.
28. Sur R, Babad JM, Garay M, et al. Anti-inflammatory activity of sertaconazole nitrate is mediated via activation of a p38/COX-2/PGE2 pathway. *J Invest Dermatol*. In press.
29. Liebel F, Lyte P, Garay M, et al. Anti-inflammatory and anti-itch activity of sertaconazole nitrate. *Arch Dermatol Res*. 2006;298:191-199.
30. Pfaller MA, Sutton DA. Review of in vitro activity of sertaconazole nitrate in the treatment of superficial fungal infections. *Diagn Microbiol Infect Dis*. 2006;56:147-152.
31. Carrillo-Muñoz AJ, Guglietta A, Palacin C, et al. In vitro antifungal activity of sertaconazole compared with nine other drugs against 250 clinical isolates of dermatophytes and *Scopulariopsis brevicaulis*. *Chemotherapy*. 2004;50:308-313.
32. Carillo-Muñoz AJ, Guisiano G, Ezkurra PA, et al. Sertaconazole: updated review of a topical antifungal agent. *Expert Rev Anti Infect Ther*. 2005;3:333-342.
33. Farre M, Ugena B, Badenas JM, et al. Pharmacokinetics and tolerance of sertaconazole in man after repeated percutaneous administration. *Arzneimittelforschung*. 1992;42:752-754.
34. Palacin C, Tarrago C, Ortiz JA. In vitro activity of sertaconazole against *Malassezia furfur* and pachydermatis in different culture media. *Methods Find Exp Clin Pharmacol*. 1998;20:451-455.
35. Savin R, Jorizzo J. The safety and efficacy of sertaconazole nitrate cream 2% for tinea pedis. *Cutis*. 2006;78:268-274.
36. Collier CN, Cantrell WC, Elewski BE. Within the fold: treatment of intertrigo. Poster presented at: 65th Annual Meeting of the American Academy of Dermatology; February 2-6, 2007; Washington, DC.
37. Goday JJ, Yanguas I, Aguirre A, et al. Allergic contact dermatitis from sertaconazole with cross-sensitivity to miconazole and econazole. *Contact Dermatitis*. 1995;32:370-371.