



CLINICAL UPDATE

Topical Azole Antimycotics for Superficial Fungal Infections

The American Academy of Dermatology guidelines for the care of superficial mycotic infections of the skin estimate that 10% to 20% of the US population is infected by a dermatophyte, and, of these infections, tinea pedis is the most commonly occurring dermatophyte infection, affecting up to 70% of adults [J Am Acad Dermatol. 1996;34:282-286]. The most commonly implicated dermatophyte organisms in the United States are *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Trichophyton tonsurans*. *Trichophyton verrucosum*, *Microsporum canis*, *Microsporum gypseum*, and *Epidermophyton floccosum* are also the source of numerous infections [J Am Acad Dermatol. 1996;34:282-286].

Infections caused by *Candida* species are the most frequently occurring yeast infections in humans [Antimicrob Agents Chemother. 2003;47:956-964]. *Candida albicans* is the most common causal yeast of candidiasis, but *Candida glabrata*, *Candida tropicalis*, *Candida krusei* [Clin Microbiol Rev. 1996;9:499-511; Antimicrob Agents Chemother. 2003;47:956-964] and *Malassezia furfur* [Methods Find Exp Clin

Pharmacol. 1998;20:451-455] are other yeasts that are commonly involved in fungal infections.

There are a variety of topical antifungal agents available for the treatment of superficial fungal infections, many differing in their spectrum of activity and vehicle availability. The polyenes (eg, nystatin) are effective against *Candida* species. The allylamines/benzylamines (eg, naftifine, terbinafine, butenafine) have varying activity against dermatophytes and *Candida* species, whereas the imidazoles (eg, clotrimazole, econazole, ketoconazole, miconazole, sulconazole, oxiconazole, sertaconazole) have varying activity against dermatophytes, *Candida* species, and *M. furfur* [J Am Acad Dermatol. 1997;36:S3-S8; Diagn Microbiol Infect Dis. 2006;56:147-152]. Because of their broad-spectrum activity, azole antifungals are used commonly to treat superficial fungal infections, and because yeast infections caused by *C. albicans* do not respond as well to allylamines, azole antifungals are often preferred in these types of infections [Am J Clin Dermatol. 2004;5:443-451].



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Azoles: Mechanism of Action

Although the exact mechanism of action of azole antifungals is not known, it is believed that they act primarily by inhibiting ergosterol biosynthesis by selectively inhibiting cytochrome P-450 enzymes. Ergosterol is a key constituent of the cell membrane of fungi, and inhibition of ergosterol biosynthesis leads to fungal cell injury, primarily by the leakage of intracellular components from the cell [Physicians' Desk Reference. 60th ed. Montvale, NJ: Thomson; 2006:2383-2384].

Structure and Absorption Characteristics

Sertaconazole nitrate is designed chemically as (±)-1-[2,4-dichloro-β,[(7-chlorobenzo[*b*]thien-3-yl)methoxy]phenethyl]imidazole nitrate and has a molecular weight of 500.8 [Physicians' Desk Reference. 60th ed. Montvale, NJ: Thomson; 2006:2383-2384]. Sertaconazole is synthesized with a lipophilic benzothiophene ether, which enhances the penetration

of the drug through the horny layer of the skin where some pathogenic fungi thrive, but avoids systemic absorption [Diagn Microbiol Infect Dis. 2006;56:147-152; Arzneimittelforschung. 1992;42:752-754].

Furthermore, therapeutic concentrations of sertaconazole persist in the skin for a prolonged duration. Farré and colleagues showed that the percentage of cutaneous absorption 24 hours after application was 72% of the applied dose, and plasma analysis showed no detectable sertaconazole concentrations at a quantitation limit of 25 ng/mL [Arzneimittelforschung. 1992;42:752-754]. Palacin and colleagues found similarly positive results in a cutaneous retention time test, in which it was demonstrated that sertaconazole 2% cream has an excellent and proportional antifungal effect at 12, 24, or 48 hours after application and showed statistically significant differences in clinical values versus its comparator formulation bifonazole [J Mycol Med. 1995;5:35-39].

Although additional study into the clinical benefits of sertaconazole's absorption characteristics is warranted, it is possible that sertaconazole's prolonged dermal retention could translate into less frequent application in clinical practice, a concept that is supported by studies demonstrating the efficacy of sertaconazole with once-daily dosing [Clin Drug Invest. 2003;23:387-394; Clin Ther. 1995;17:264-269]. Furthermore, because of sertaconazole's epidermal reserve, its efficacy with less frequent dosing could improve patient compliance with therapy and may support its use for maintenance therapy.

Dual Mechanism of Action

Sertaconazole nitrate belongs to the imidazole class of antifungal agents. Sertaconazole, like other imidazoles, has two modes of action (ie, fungista-

tic and fungicidal) [Arzneimittelforschung. 1992;42:721-724]. Sertaconazole derives its fungistatic activity from the inhibition of cytochrome P-450-dependent ergosterol synthesis, which interferes with fungal cell growth [Arzneimittelforschung. 1992;42:721-724; Diagn Microbiol Infect Dis. 2006;56:147-152]. Secondly, sertaconazole binds to nonsterol lipids and impedes the regulation of fungal cell membranes; this leads to leakage of intracellular components including adenosine triphosphate, which causes immediate cell death [Diagn Microbiol Infect Dis. 2006;56:147-152].

Like other azoles, sertaconazole inhibits ergosterol biosynthesis in direct proportion to the concentration of the drug that is used, but because of its mixed structure, sertaconazole can cause direct damage to the *C. albicans* cell membrane, which is the basis of its significant fungicidal effect against this organism [Arzneimittelforschung. 1992;42:718-720; Arzneimittelforschung. 1992;42:705-710; Arzneimittelforschung. 1992;42:721-724]. Because of its dual mechanism of action, sertaconazole is an effective fungistatic and fungicidal agent.

Broad-Spectrum Activity

Sertaconazole is a broad-spectrum antifungal agent that is effective against common pathogens affecting the skin and mucous membranes and is indicated in the United States and Europe for various dermatophyte infections, mucocutaneous candidiasis, and tinea versicolor, as well as secondary indications for the treatment of *Trichomonas* infections and infections caused by gram-positive bacteria, which occur secondary to fungal infections. Sertaconazole has demonstrated activity against numerous pathogenic organisms, a partial list of which can be found in Table 1 (on page 2) [Diagn Microbiol Infect Dis. 2006;56:147-152].

ACCREDITATION

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Elsevier Office of Continuing Medical Education (EOCME) and SKIN & ALLERGY NEWS. The EOCME is accredited by the ACCME to provide continuing medical education (CME) for physicians.

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Term of Approval: May 2007–May 31, 2008.

TARGET AUDIENCE

Dermatologists, podiatrists, and other health care professionals who treat patients diagnosed with superficial fungal infections.

EDUCATIONAL NEEDS

The management of superficial fungal infections can be a significant challenge for clinicians working in the dermatology, primary care, and podiatric patient care settings. Although there are a variety of topical antifungal agents available to treat superficial mycoses, treatment is complicated by many factors, including the increasing incidence and pathogenicity of many fungal microorganisms, reduced sensitivity to traditional antifungal agents, the limited spectra of some therapies, and patient noncompliance with therapy. Furthermore, there are numerous antifungal agents that have demonstrated efficacy in one or more fungal indications, but the majority of these are now available only in generic formulations, which may be limited by product instability and/or decreased cosmetic acceptability. This article will provide an overview of the imidazole class of azole antifungal agents with a focus on sertaconazole. Sertaconazole is a broad-spectrum antifungal agent with antibacterial, antipruritic, and anti-inflammatory/anti-itch properties that is currently indicated for tinea pedis in the United States but has broader therapeutic indications in Europe.

LEARNING OBJECTIVES

After completing this educational activity, participants should be able to:

- List the groups of organisms against which azole antifungals are active and realize the breadth of sertaconazole's activity against various organisms involved in superficial fungal infections
- Understand how the absorption characteristics of sertaconazole could translate into therapeutic benefit
- Describe sertaconazole's dual mechanism of action and what makes it unique among azole antifungals
- Recognize the role of bacterial colonization in some fungal infections such as tinea pedis and intertrigo
- Discuss the in vitro and in vivo anti-inflammatory effects of sertaconazole
- Appreciate sertaconazole's clinical efficacy and safety in gynecologic conditions and dermatologic conditions other than tinea pedis.

FACULTY DISCLOSURES

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James Q. Del Rosso, DO: Dr Del Rosso has served as a consultant, speaker, and researcher for Amgen, Coria, CollaGenex, Galderma, Graceway, Intendis, Medicis, Novartis, OrthoNeutrogena, Stiefel, and Warner-Chilcott, has served as a researcher for QLT, and has served as a consultant and speaker for SkinMedica.

Educational Reviewer: **Ronald Miller, PhD**, had nothing to disclose.

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Sertaconazole has demonstrated good in vitro activity against pathogenic yeasts [J Chemother. 1999;11:187-190; Chemotherapy. 1997;43:387-392; J Antimicrob Chemother. 1996;37:815-819; Chemotherapy. 1996;42:112-117; J Antimicrob Chemother. 1995;36:713-716] that include dermatophyte fungi [Chemotherapy. 1997;43:387-392; J Chemother. 2003;15:555-557; Chemotherapy. 2003;49:248-251], Malassezia species [Methods Find Exp Clin Pharmacol. 1998;20:451-455; Arzneimittelforschung. 1992;42:705-710], and opportunistic filamentous fungi [Arzneimittelforschung. 1992;42:705-710; Arzneimittelforschung. 1992;42:699-705]. Furthermore, sertaconazole has not been associated with antifungal resistance issues like some available antifungal agents; Carrillo-Muñoz and colleagues showed that sertaconazole's activity against dermatophytes includes 114 isolates of 12 fungal dermatophyte species with low susceptibility to the oral triazole fluconazole [Chemotherapy. 2003;49:248-251].

Carrillo-Muñoz and Tur-Tur also have demonstrated that sertaconazole's antifungal activity is comparable to and often greater than that of other antifungal agents. Table 2 shows the minimum inhibitory concentration (MIC) values for sertaconazole, bifonazole, and the allylamine antifungal terbinafine [Chemotherapy. 1997;43:387-392]. Investigators found that sertaconazole was statistically more active than were bifonazole and terbinafine for Candida strains, with sertaconazole's MIC values testing lower against each yeast species than those of bifonazole and terbinafine. Terbinafine was more active against dermatophytes than were sertaconazole and bifonazole, with the MICs of sertaconazole and bifonazole being lower with Epidermophyton floccosum and Trichophyton rubrum than for other dermatophytes.

These results are similar to those from other reports that found higher or comparable in vitro activity when assessing sertaconazole versus other azoles, including ketoconazole, bifonazole, miconazole, econazole, and clotrimazole, against numerous causative organisms of fungal infections [J Antimicrob Chemother. 1995;36:713-716; J Antimicrob Chemother. 1996;37:815-819; Arzneimittelforschung. 1992;42:711-714]. There are numerous data supporting sertaconazole's broad-spectrum antifungal activity, which occurs at concentrations that are significantly lower than those reached with the topical application of sertaconazole [Expert Rev Anti Infect Ther. 2005;3:333-342].

In Vitro Fungicidal Activity

Like other azoles, sertaconazole is fungistatic when used in lower concentrations, and its activity is in a similar or higher range than that of miconazole and clotrimazole [Arzneimittelforschung. 1992;42:705-710; J Antimicrob Chemother. 1996;37:815-819; Arzneimittelforschung. 1992;42:711-714; Methods Find Exp Clin Pharmacol. 2001;23:61-64], but when used at concentrations between 0.5 µg/mL and 16 µg/mL, it has a 90% fungicidal effect [Arzneimittelforschung. 1992;42:711-714].

Sertaconazole has demonstrated good fungicidal activity in vitro against Candida [Arzneimittelforschung. 1992;42:699-705; Arzneimittelforschung. 1992;42:705-710; Chemotherapy. 1996;42:112-117], which is an especially important differentiator of sertaconazole because many azoles are only fungistatic [Antimicrob Agents Chemother. 2003;47:956-964].

One limitation of purely fungistatic agents is that they may allow fungi to persist in fomites, which could lead to reinfection. In addition to providing eradication of the organism, fungicidal agents such as sertaconazole may have the advantage of reducing the chance of reinfection because they can eliminate the fungi that chronically contaminate footwear, floors, and shower basins [Am J Clin Dermatol. 2004;5:443-451].

Antibacterial Activity

Sertaconazole has demonstrated in vitro antibacterial activity against the staphylococci, streptococci, Gardnerella vaginalis, and other bacteria involved in mixed infections [Int J Gynaecol Obstet. 2000;71(suppl 1):S37-S46; Arzneimittelforschung. 1992;42:699-705]. The activity of sertaconazole against gram-positive bacteria was described at a mean MIC value of 0.97 µg/mL, which was considered therapeutically relevant [Arzneimittelforschung. 1992;42:699-705]. This means that sertaconazole has antibacterial activity against gram-positive bacteria that typically colonize cutaneous fungal infections such as interdigital tinea pedis, which can exacerbate regional inflammation, lesion appearance, and clinical symptoms [Cutis. 2006;78:268-274]. Furthermore, sertaconazole demonstrated superior activity against the most important vaginal isolate, Gardnerella, compared with clotrimazole and fluconazole, both of which are inactive against this organism [Int J Gynaecol Obstet. 2000;71:S37-S46].

In order to clarify the role of bacteria in dermatophyte infections, Leyden and Kligman performed a comprehensive study in the 1970s on the interaction of dermatophytes and resident bacteria in interdigital tinea pedis, commonly referred to as "athlete's foot" [Arch Dermatol. 1978;114:1466-1472]. These investigators confirmed the observation that the increasing severity of athlete's foot is characterized by a decline in the population of fungi with a corresponding increase in bacterial growth. Investigators also compared the efficacy of antifungal monotherapy, antibacterial

monotherapy, and combined therapy. They demonstrated that the use of an antifungal alone was effective in the dry, scaling form of tinea pedis (dermatophytosis simplex), but not in the wet, macerated form (dermatophytosis complex), and the reverse was true when an antibacterial agent alone was used. This pattern of relative fungal and bacterial proliferation makes logical sense as many bacteria favor a moist, macerated growth environment. However, the combination of an antifungal agent and an antibacterial agent was the most effective treatment in both forms and produced a faster and greater resolution of signs and symptoms than did the use of either agent alone.

Although further study is needed to clarify the added benefit of sertaconazole's antibacterial activity in the treatment of mycoses that present with superinfection, it has long been observed that bacteria play a contributory role in certain superficial mycoses, and the antibacterial effects of sertaconazole could have important benefits in terms of efficacy and length of treatment.

In Vivo and In Vitro Anti-Inflammatory Activity

Superficial fungal infections are often associated with an inflammatory component that can cause irritation, itching, and/or stinging/burning, and antifungal agents with intrinsic anti-inflammatory activity may have the potential to provide clinical benefit in addition to the eradication of fungi. It has been demonstrated that an antifungal/corticosteroid combination product containing clotrimazole and betamethasone can provide anti-inflammatory clinical benefit beyond the eradication of the dermatophytes [Cutis. 1982;30:258-261]. However, the long-term topical application of a corticosteroid, including its use in combination with an antifungal agent, has been associated with local adverse effects, including atrophy and striae. [Skin Therapy Lett. 1999;4:1-5; J Am Acad Dermatol. 1987;17:518-519]. Because of these concerns, nonsteroidal therapeutic options are optimal for the safe and effective treatment of inflammation secondary to superficial fungal infections.

Sertaconazole has demonstrated in vitro and in vivo anti-inflammatory activities in addition to its antifungal and antibacterial properties. Agut and colleagues assessed the anti-inflammatory activity of 2% sertaconazole nitrate to rats using the croton oil-induced edema test [Methods Find

Table 2. Antifungal Activity (mg/L) of Bifonazole, Sertaconazole, and Terbinafine Against Yeasts and Dermatophyte Fungi

| Fungi | Bifonazole MIC | Sertaconazole MIC | Terbinafine MIC |
|---|-------------------|----------------------|--------------------|
| Candida albicans (81) | 3.51 | 1.14 | 9.59 |
| Candida famata (1) | 10 | 0.03 | 0.15 |
| Candida glabrata (22) | 4.15 | 0.66 | 19.9 |
| Candida guilliermondii (5) | 3.25 | 0.41 | 7 |
| Candida humicola (1) | 20 | 5 | 20 |
| Candida intermedia (1) | 10 | 2.5 | 40 |
| Candida krusei (14) | 1.87 | 0.77 | 12.89 |
| Candida parapsilosis (25) | 3.05 | 0.26 | 2.53 |
| Candida tropicalis (27) | 8.93 | 1.49 | 11.89 |
| Mean for Candida species (177) | 7.20 | 1.36 | 13.77 |
| Cryptococcus neoformans (3) | 0.67 | 0.12 | 2.18 |
| Mean for yeasts (180) | 6.54 | 1.24 | 12.61 |
| Epidermophyton floccosum (7) | 0.2 | 0.11 | 0.03 |
| Microsporum canis (9) | 1.73 | 0.27 | 0.17 |
| Microsporum gypseum (5) | 2.25 | 0.93 | 0.03 |
| Microsporum audouinii (1) | 2.5 | 0.31 | 0.03 |
| Trichophyton mentagrophytes (14) | 1.91 | 0.77 | 0.03 |
| Trichophyton rubrum (17) | 0.18 | 0.09 | 0.03 |
| Mean for dermatophytes (53) | 1.04 | 0.41 | 0.05 |

MIC, minimum inhibitory concentration. Adapted with permission from Carrillo-Muñoz AJ, Tur-Tur C. Chemotherapy. 1997;43:387-392. Permission also from S. Karger AG, Basel.

Exp Clin Pharmacol. 1996;18:233-234], and they demonstrated that cutaneous administration of sertaconazole resulted in a 39.8% reduction in edema.

More recently, Liebel and colleagues compared the anti-inflammatory activities of butoconazole, ciclopirox olamine, fluconazole, miconazole nitrate, sertaconazole nitrate, terconazole, tioconazole, and ketoconazole in a number of in vivo and in vitro preclinical models of cutaneous inflammation and pruritus [Arch Dermatol Res. 2006;298:191-199]. In an in vitro model that assessed the inhibitor effects of antifungals on phytohemagglutinin-stimulated release of cytokines from human peripheral blood lymphocytes, these investigators showed that sertaconazole nitrate was significantly more active than the other antifungals against the release of all cytokines tested (P<0.05).

In an in vivo model from the same series of experiments, investigators found that sertaconazole demonstrated a significant reduction (50.7% in irritant dermatitis in a tetradecanoyl phorbol acetate-induced ear edema model (P<0.05). Although butoconazole and ketoconazole also demonstrated a significant reduction in irritant dermatitis (37.9% and 33.1%, respectively), sertaconazole nitrate was more active in this model. The positive control was bethamethasone-17 valerate (0.1%), which reduced inflammation by 66.9%. In another experiment, these investigators showed that sertaconazole inhibited contact hypersensitivity by 49.7% in an oxazolone-induced ear edema model (P<0.05). They also demonstrated a statistically significant reduction (38.7%) in scratching responses (P<0.05) in a murine model of pruritus. This reduction in scratching in sertaconazole-treated animals was

comparable to the reduction in scratching in hydrocortisone 1%-treated animals (43.5%).

The results of these experiments show that the topical administration of sertaconazole nitrate has significant anti-inflammatory/antipruritic activities in a variety of cutaneous inflammation models and underscore the importance of further investigation into the potential of sertaconazole and other broad-spectrum antifungals with anti-inflammatory activity as a corticosteroid-sparing approach to therapy in the treatment of superficial mycoses with inflammation.

Clinical Use in Dermatology

Sertaconazole is currently approved in the United States for the topical treatment of interdigital tinea pedis in immunocompetent patients 12 years of age or older; however, this agent has demonstrated efficacy in other cutaneous mycoses, seborrheic dermatitis, tinea (pityriasis) versicolor, and vaginal candidiasis and is currently being evaluated for other indications, mostly outside of the United States. Sertaconazole is available in a 2% cream in the United States, but this antifungal also is marketed in 48 other countries [National PBM Drug Monograph. Sertaconazole (Ertaczo™). April 2004] for application once or twice daily in gel, powder, and solution formulations applicable for dermatologic disorders, as well as a vaginal cream, ovules, or tablets for gynecologic use [Int J Gynaecol Obstet. 2000;71 (suppl 1):S3-S20].

Tinea Pedis

The safety and efficacy of topical sertaconazole nitrate 2% cream in the treatment of interdigital tinea pedis

Table 1. Broad-Spectrum Activity of Sertaconazole

| | |
|---|---|
| Dermatophytes | <ul style="list-style-type: none"> • <i>Trichophyton rubrum</i> • <i>Trichophyton mentagrophytes</i> • <i>Epidermophyton floccosum</i> |
| Mucocutaneous candidiasis | <ul style="list-style-type: none"> • <i>Candida albicans</i> • <i>Candida glabrata</i> • <i>Candida krusei</i> • <i>Candida parapsilosis</i> • <i>Candida tropicalis</i> |
| Pityrosporiasis (tinea versicolor) | <ul style="list-style-type: none"> • <i>Malassezia furfur</i> |
| Gram-positive bacteria | <ul style="list-style-type: none"> • <i>Staphylococci</i> • <i>Streptococci</i> |

Source: Pfaller MA, Sutton DA. Diagn Microbiol Infect Dis. 2006;56:147-152.

were evaluated in two randomized, multicenter, double-blind, parallel-group, vehicle-controlled studies [*Cutis*. 2006;78:268-274]. A total of 588 subjects were enrolled of whom 349 completed the study. Subjects were randomized to treatment with sertaconazole or vehicle applied twice daily for 4 weeks. Investigator-assessed global evaluations of clinical response were performed at weeks 1, 2, 3, 4, and 6, and subjects were also asked to evaluate treatment efficacy and cosmetic acceptability at week 4.

Investigator periodic global evaluation of clinical signs and symptoms showed that sertaconazole-treated subjects achieved a statistically higher percentage of overall clinical success than did vehicle-treated subjects at weeks 4 (57.9% vs 39.9%, respectively; $P < 0.0009$) and 6 (64.6% vs 37.8%, respectively; $P < 0.0001$). Subject evaluations indicated rapid symptom relief after 1 week, with 77% of active-treatment subjects reporting either mild or no itching compared with only 20% of subjects at baseline. At week 3, a significantly greater percentage of subjects using active treatment were itch-free than that of vehicle-treated subjects (64% vs 44%, respectively; $P = 0.0001$), and this difference remained statistically superior through week 6 (76.4% vs 51.1%, respectively; $P < 0.0001$).

Efficacy results showed that a significantly higher percentage of sertaconazole-treated subjects than that of vehicle-treated subjects achieved mycologic cure, defined as negative potassium hydroxide (KOH) preparation and fungal culture tests at weeks 4 and 6 ($P < 0.0001$). Importantly, a sertaconazole mycologic cure rate of 66.2% was sustained 2 weeks post-treatment, which was three times higher than the mycologic cure rate in the vehicle-treated group ($P < 0.0001$). Furthermore, 89% of sertaconazole-treated subjects had negative cultures versus 38% of vehicle-treated subjects ($P < 0.0001$). The relapse rate, which reflected the percentage of subjects who had a successful treatment outcome at week 4 but were assessed as clinical failures at week 6, was significantly lower in the sertaconazole group than in controls (29.5% vs 66.7%, respectively; $P < 0.0001$). The rates of cutaneous adverse events (AEs) were comparable between active- and vehicle-treatment groups. Sertaconazole nitrate 2% cream is an effective, safe, and well-tolerated treatment for interdigital tinea pedis.

Cutaneous Mycoses: Sertaconazole Versus Miconazole

Alomar and colleagues assessed the efficacy, safety, and tolerability of sertaconazole 2% cream versus miconazole 2% cream twice daily for 28 days in 631 subjects with various types of cutaneous mycoses, including tinea pedis, tinea corporis, tinea barbae, tinea manuum, and tinea cruris [*Arzneimittelforschung*. 1992;42:767-773]. Clinical assessment was performed at six checkups from day 0 to day 35, and safety and tolerability were evaluated with blood test analyses and patient self-assessment of tolerability and AEs. Of the 631 subjects enrolled, 569 subjects completed the trial (sertaconazole [n=295], miconazole [n=274]). Results showed that sertaconazole demonstrated greater therapeutic efficacy than did miconazole, but the difference was not statistically significant. However, in the actuarial curve of clinical improvement, investigators found that sertaconazole-treated subjects achieved the category of "clinically cured" sooner and more often than did miconazole-treated subjects from the fourth checkup on, a difference that was statistically significant ($P < 0.05$).

In this same study, microscopic examination at the third checkup showed that 79.2% of miconazole-treated subjects and 86.8% of sertaconazole-treated subjects were negative, which was a statistically significant difference ($P < 0.02$), and the percentage of subjects with negative microscopy increased to 94.2% and 98.3% at the fifth checkup, respectively, with this difference being statistically significant in favor of sertaconazole ($P < 0.01$). By the sixth checkup, the difference in microscopic test performance between the two agents favored sertaconazole, but this was not statistically significant. Regarding the assessment of relapse, there was a highly significant difference ($P = 0.001$) in the rate of relapse assessed at the sixth checkup between sertaconazole (4.4% [n=13]) and miconazole (11.9% [n=33]). Safety assessments for both drugs were excellent, but sertaconazole demonstrated better tolerance with five cases of contact dermatitis in the miconazole group, but no cases of contact dermatitis in the sertaconazole group.

These results demonstrate that sertaconazole is a potent antifungal agent that is able to achieve mycologic cure in

a large proportion of subjects in each type of clinical presentation in a shorter period of time than does miconazole. These data suggest that sertaconazole treatment could be associated with greater patient compliance with therapy because of its more rapid mycologic cure and favorable tolerability.

Patient Adherence to Antifungal Therapy

Patient adherence to a therapeutic regimen is an important concern when treating dermatomycoses and other dermatologic conditions. Two important factors that may increase the likelihood of poor patient compliance with therapy is the need for greater frequency of application, which is less convenient, and premature discontinuation of therapy due to a lack of tolerability or unsatisfactory vehicle attributes. In a German study, Meinhof and colleagues performed a survey among dermatologists, general practitioners, and patients that assessed noncompliance with topical antimycotic therapies [*Dermatologica*. 1984;169(suppl 1):57-66]. Investigators found that 48% of patients did not adhere to the daily dosage schedule, 44% reduced the number of daily applications, 4% increased the number of applications, and 25% stopped treatment after their symptoms had disappeared. These investigators concluded that enhancing patient compliance with antifungal therapy could be achieved by providing improved doctor-patient communication and by providing antifungal therapy that minimizes non-compliance by requiring less frequent applications and shorter treatment times.

Efficacy and Tolerability in Pediatric Patients With Dermatophyte Infections

Sertaconazole has also demonstrated efficacy in the treatment of various dermatophyte infections in a pediatric population. Van Esso and colleagues assessed the efficacy and tolerability of once-daily sertaconazole 2% cream for 2 weeks in 29 children, and 16 of these patients with culture-confirmed cutaneous mycoses were assessed for efficacy [*Clin Ther*. 1995;17:264-269]. Efficacy and tolerability assessments were made at weeks 1, 2, and 4. The ages of these patients ranged from 2 to 16 years; 14 of these patients had tinea corporis, one had tinea cruris, and one had tinea pedis.

Results showed that clinical cure was achieved after 1 week in 31% of patients, after 2 weeks in 75% of patients, and after 3 weeks in 100% of patients. Furthermore, the drug was very well tolerated in all 29 patients who were treated and assessed for tolerability, and none of the patients experienced local or systemic AEs. These results further support the efficacy of once-daily dosing and complement in vitro data that demonstrate good penetration and persistence of sertaconazole in the skin [*Arzneimittelforschung*. 1992;42:752-754].

Seborrheic Dermatitis and Tinea Versicolor

Although its exact role has yet to be defined, *Malassezia* species play a role in the etiology of various skin diseases, including seborrheic dermatitis, tinea (pityriasis) versicolor,

and folliculitis by *M. furfur*. [*Methods Find Exp Clin Pharmacol*. 1998;20:451-455]. As noted above, sertaconazole has demonstrated good in vitro activity against *M. furfur* [*Arzneimittelforschung*. 1992;42:705-710], which correlates with the drug's clinical efficacy in seborrheic dermatitis and tinea (pityriasis) versicolor.

Two European studies investigating the safety and efficacy of sertaconazole in seborrheic dermatitis were recently reviewed by Torres and Camps [*Int J Gynaecol Obstet*. 2000;

71(suppl 1):S3-S20]. The first study assessed the efficacy of sertaconazole 2% gel versus placebo in the treatment of seborrheic dermatitis of the scalp in 15 male and female adult subjects. Sertaconazole gel was applied once daily every 3 days for 4 weeks. Results showed that sertaconazole-treated patients demonstrated a statistically significant decrease in the severity of the clinical signs of desquamation and symptoms of pruritus, as well as a statistically significant decrease in dermatitis. Impor-

THE IMPACT OF GENERIC SUBSTITUTION ON THERAPEUTIC OUTCOMES

Generic substitution is a factor that may have an impact on a patient's adherence to topical antifungal therapy. Currently, the majority of topical antifungal agents are available as generic formulations. This has raised questions regarding the efficacy, tolerability, and cosmetic acceptability of these agents. Generic substitution requires only that the active ingredients approximate those of the brand name but often ignores the major role that vehicle composition plays in the effectiveness and patient acceptability of a topical formulation. The vehicle of any given topical formulation comprises up to 99.975% of the product's composition and plays a substantial role in the cutaneous delivery of the active ingredient, the potency of an agent, and the patient's adherence to therapy [*J Am Acad Dermatol*. 1998;39:S67-S73].

For generic substitution to be effective, it is necessary that the generic drug have pharmaceutical (therapeutic) equivalence, bioequivalence, and bioavailability to the brand-name drug, with comparable standards of quality and purity (Table 3) [*J Am Acad Dermatol*. 1998;39:S67-S73]. However, generic drugs may differ in the use of inert ingredients, packaging, shelf life, and manufacturing, which may disregard the important role of the vehicle and eliminate the interchangeability of the generic and brand-name formulations (Table 3). Differences in the inert ingredients in the vehicle could cause skin irritation, allergic reactions, or inadequate response to a topical formulation [*J Am Acad Dermatol*. 1998;39:S67-S73] in patients who tolerated and/or had good response to the brand-name product.

Generic substitution could also result in therapeutic failure of a topical treatment, which is an especially important consideration because this could be interpreted by the clinician as the need for a more potent drug (eg, a systemic agent) or a longer course of treatment, rather than recognizing the failure as a bioequivalence issue [*J Am Acad Dermatol*. 1998;39:S67-S73]. Furthermore, a lack of equivalence of the vehicle in a generic formulation could impact the penetration and absorption of the active agent into the skin, which could affect how well the active drug performs [*J Am Acad Dermatol*. 1998;39:S67-S73].

In conclusion, the clinician needs to be aware that the vehicle of most topical drugs comprises the majority of the formulation and that variations in the inert ingredients among different generic formulations may have a substantial impact on the drug's absorption, efficacy, and tolerability, and the patient's acceptance of an antifungal formulation. When using a generic formulation, one must consider that insufficient response or lack of tolerability may be due to a bioequivalence or formulation problem of the generic rather than inefficacy of the drug. Depending on the clinical scenario, the clinician may consider switching to a name-brand antifungal before trying a more potent therapeutic agent or prolonging therapy with the generic product.

Table 3. Measures Used to Evaluate the Interchangeability of Drugs

Pharmaceutical equivalence

Comparison of the therapeutic efficacy and toxicity profile of two different drug products given by the same dosage regimen to patients being treated with the drug product.

| Constant | Variable |
|---|--|
| <ul style="list-style-type: none"> • Active ingredient • Strength • Route of administration • Dosage form | <ul style="list-style-type: none"> • Inert ingredients • Color • Packaging • Shelf life • Manufacturing process |

Biological equivalence

A comparison of the relative bioavailability of two different drug products in the same test population.

Bioavailability (systemic)

The rate and extent to which an active ingredient is absorbed from the site of administration and reaches the systemic circulation.

Adapted with permission from Piacquadro D, Kligman A. *J Am Acad Dermatol*. 1998;39:S67-S73.

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tantly, among those subjects with severe disease at baseline, the placebo-treated subjects showed no clinical improvement, whereas those treated with sertaconazole exhibited considerable improvement.

The second study reviewed by Torres and colleagues assessed the efficacy and safety of sertaconazole 2% gel versus ketoconazole 2% gel in 60 male and female subjects with seborrheic dermatitis of the scalp. Subjects were treated with either sertaconazole or ketoconazole every 3 days for 28 days. Treatment outcomes were assessed on days 0, 14, and 28 using a visual analogue scale that included measurements of erythema, itching, and scaling. Symptoms and AEs were also evaluated.

Results showed that treatment with sertaconazole for 28 days demonstrated considerable improvement in symptoms, and clinical improvement in sertaconazole-treated subjects was superior to improvement in those subjects treated with ketoconazole. Furthermore, no subjects withdrew from the trial because of AEs. These results indicate that sertaconazole is effective for the treatment of seborrheic dermatitis.

Tinea (pityriasis) versicolor is another common superficial skin infection caused by *M. furfur*, which presents as either hypopigmented or hyperpigmented, well-demarcated macules that are characterized by a fine, flaky (pityriasisiform) scale [*J Dermatolog Treat*. 2004;15:189-192]. Tinea versicolor most often affects adults and is generally worse in geographic areas with tropical ambient temperatures [*J Am Acad Dermatol*. 1996;34:287-289]. Treatment includes topical antifungal products (eg, imidazoles, ciclopirox olamine, and various shampoos and lotions containing selenium sulfide, zinc pyrithione, sulfur, salicylic acid, propylene glycol, or benzoyl peroxide), and oral antifungal therapy with ketoconazole, fluconazole, or itraconazole is indicated for patients with extensive involvement or recurrent infections [*J Am Acad Dermatol*. 1996;34:287-289].

Nasarre and colleagues assessed the activity of sertaconazole in 21 subjects with tinea versicolor confirmed by KOH microscopy and Wood's light examination [*Arzneimittelforschung*. 1992;42:764-767]. Eleven subjects were treated with sertaconazole 1% cream, and 10 subjects were treated with sertaconazole 2% cream twice daily for 4 weeks. Each of the 21 subjects achieved a quick, safe, and effective cure, with no significant differences between the two treatment groups. However, the authors noted that there is a general trend in topical azole studies showing that as the size of a study population increases, the percentage of cured patients is substantially higher in subjects treated with a higher-concentration antimycotic agent, which likely would have been the trend in this study with a larger study population. Nevertheless, sertaconazole appears to be a very effective and safe treatment for tinea versicolor.

The Treatment of Intertrigo

Intertrigo is a cutaneous inflammatory process of the skin folds caused by friction from opposing skin surfaces

that can lead to complications such as secondary bacterial and/or fungal infections [*Am Fam Physician*. 2005;72:833-838]. Intertrigo starts as mild erythema that can progress to more intense inflammation, erosions, oozing, exudation, and crusting, with pain, burning, and itching in the affected areas [*Dermatol Nurs*. 2004;16:43-57].

The moist, damaged skin associated with intertrigo is a breeding ground for bacteria and/or fungi. Secondary bacterial infections can be caused by *Staphylococcus aureus* either alone or with group A β -hemolytic streptococci, and *Pseudomonas aeruginosa*, *Proteus mirabilis*, or *Proteus vulgaris* may also exacerbate intertrigo [*Am Fam Physician*. 2005;72:833-838].

Secondary fungal infections also are commonly associated with intertrigo. *Candida* is a common causative organism, but dermatophytes (eg, *T. rubrum*, *T. mentagrophytes*, *E. floccosum*) have also been linked to this infection. Dermatophyte and bacterial infections can occur together in interdigital intertrigo, and yeasts also are commonly found in the interdigital areas. Seborrheic dermatitis also occurs within the skin folds, but it is unclear if intertrigo complicated by *Malassezia* species is a distinct disease entity [*Am Fam Physician*. 2005;72:833-838]. In addition, a common sign of secondary infection is highly prominent inflammation [Collier CN et al. Poster presented at: 65th Annual Meeting of the American Academy of Dermatology; February 2-6, 2007; Washington, DC].

Sertaconazole has demonstrated broad-spectrum activity against dermatophytes, *Candida* species, and *Malassezia* species, and it has inherent anti-inflammatory, anti-itch, and antibacterial properties that are useful in the treatment of intertrigo. Patients with various types of intertrigo have been successfully treated with sertaconazole at the University of Alabama at Birmingham clinic (Table 4) [Collier CN et al. Poster presented at: 65th Annual Meeting of the American Academy of Dermatology; February 2-6, 2007; Washington, DC]. Patients with intertrigo of the toe webs, groin, umbilicus, and axillae were all cleared with sertaconazole treatment, and only one patient with toe-web intertrigo and one patient with axillary intertrigo experienced mild stinging and burning. These data underscore the broad-spectrum utility of sertaconazole, as well as the usefulness of sertaconazole's anti-inflammatory and anti-itch properties, which further may improve clinical outcome for patients with intertrigo and other cutaneous infections.

Clinical Use in Gynecology

Vulvovaginal mycoses are the most common reasons for gynecologic consultation. The most common causative microorganism is *C. albicans*, which has been isolated in more than 80% of samples [*Int J Gynaecol Obstet*. 2000;71(suppl 1):S3-S20], but other *Candida* species including *C. glabrata* also have been implicated. Imidazole agents are commonly used to treat vulvovaginal mycoses, but their inadequate therapeutic response to infections caused by *C. glabrata*, in combination with the increasing re-

sistance of *C. albicans* strains, necessitates continued research into new therapeutic options [*Int J Gynaecol Obstet*. 2000;71(suppl 1):S3-S20].

Sertaconazole has an extensive efficacy and safety record in vulvovaginitis based on clinical trials performed for the registration of sertaconazole vaginal cream, tablet, and ovules, which have been examined in detail by Torres and colleagues [*Int J Gynaecol Obstet*. 2000;71(suppl 1):S3-S20]. One of these studies compared the efficacy and safety of a single-dose sertaconazole vaginal tablet (500 mg) (n=288) with the same dose of clotrimazole (n=294) in 582 subjects with mycologically confirmed vulvovaginal candidiasis [*Int J Gynaecol Obstet*. 2000;71(suppl 1):S3-S20].

Results showed that sertaconazole demonstrated greater clinical response after 7 days than did clotrimazole (36.4% vs 30.9%, respectively), and both groups achieved a cure rate of more than 80% 14 days after a single dose of either treatment. Sertaconazole was slightly superior to clotrimazole in the improvement of vulvar and cervical pruritus and erythema. Sertaconazole and clotrimazole each showed a similarly favorable safety profile. Both groups reported mild to moderate local AEs possibly related to study drug; however, investigators had difficulty differentiating these signs and/or symptoms from vulvovaginal candidiasis symptomatology.

In another comparison study, Dellenbach and colleagues assessed the efficacy and safety of sertaconazole versus econazole sustained-release suppositories in 369 women with vulvovaginal candidiasis [*Int J Gynaecol Obstet*. 2000;71(suppl 1):S47-S52]. Roughly half of the women (n=183) were treated with a 300-mg sertaconazole suppository and the other group (n=186) with a 150-mg econazole suppository. Both groups were evaluated after 1 week, and those whose infection did not resolve were treated with a second suppository and were reassessed 1 week later. End-point evaluation in all women was 1 month after the last dose. The efficacy analysis included 310 women who had a positive culture for *Candida* (sertaconazole [n=150], econazole

[n=160]). Forty-nine sertaconazole-treated women and 56 econazole-treated women were not cured after 1 week and were given a second suppository.

Efficacy results showed similar responses between the two treatment groups regarding the disappearance of signs and symptoms and mycologic cure at all time points. However, the mycologic recurrence rate after 1 month in subjects achieving a negative culture was significantly higher in the econazole group than the sertaconazole group (32.7% vs 19.8%, respectively; $P=0.035$). Local irritation was reported in both groups, but there were no serious AEs as a result of either treatment. Although there was a trend toward greater efficacy in the sertaconazole group, differences between sertaconazole- and econazole-treated subjects were not statistically significant.

Wang and colleagues assessed the efficacy, safety, and patient acceptability of a single-dose sertaconazole vaginal tablet (500 mg) compared with the 3-dose econazole vaginal tablet (150 mg) administered for 3 consecutive days in 40 patients with vulvovaginal candidiasis [*J Chin Med Assoc*. 2006;69:259-263]. Results showed that the single-dose tablet of sertaconazole demonstrated significantly greater clearance of candidiasis than did three doses of econazole based on smear method results (100% vs 72.2% on day 7, respectively; $P=0.013$, and 100% vs 77.8% on day 14, respectively; $P=0.03$). Global efficacy also demonstrated a statistically significant difference ($P=0.004$) in favor of sertaconazole; on day 7, almost 95% of sertaconazole-treated subjects had complete or advanced healing compared with 39% of econazole-treated subjects. Furthermore, sertaconazole-treated subjects had significantly greater acceptability initially than did econazole-treated subjects ($P=0.044$), although there were no differences between groups at day 14. No subjects in either group experienced AEs during the study.

Finally, Quereux and colleagues assessed the efficacy and rate of response of a single-dose sertaconazole vaginal suppository combined with sertaconazole cream applied to the vulvar area in 77 women with mycologically confirmed vulvovaginal candidiasis [*Gynecol Obstet Fertil*. 2000;28:238-244]. Subjects were randomized to treatment with either a single-dose sertaconazole suppository or the suppository combined with sertaconazole cream applied to the vulvar area for 7 days.

Results showed that the group treated with both the suppository and the cream achieved greater clinical cure rates than did the suppository-only group at day 7 (76% vs 68%, respectively) and at day 14 (100% vs 80%, respectively). Tolerance was high and similar in both groups, but symptom relief was faster in the combination group, with 78% of subjects achieving relief of pruritus as early as day 2 versus 61% in the suppository-only group, although this difference was not statistically significant. This combination treatment is associated with improved clinical cure and faster symptomatic improvement, which supports the use of the combination of sertaconazole cream with a single-dose sertaconazole suppository when candidiasis is both vaginal and vulvar.

These studies show that sertaconazole has considerable and durable antifungal effect on *Candida* species, both clinically and mycologically. Sertaconazole demonstrated efficacy that was either similar to or greater than that of the other imidazoles, econazole and clotrimazole, with faster resolution of symptoms and a favorable safety profile. Furthermore, the various vaginal formulations of sertaconazole provide options amenable to individual patient selection based on their preference, ease of use, and convenience. All of the formulations are well tolerated by patients, which could improve patient adherence to therapy.

Summary

Summary

Sertaconazole is an imidazole topical antifungal agent that has demonstrated broad-spectrum activity against numerous pathogenic organisms involved in superficial cutaneous fungal infections and vaginal candidiasis. Sertaconazole demonstrates considerable in vitro activity against pathogenic fungi and has additional anti-inflammatory and antibacterial actions that make it useful in the treatment of both polymicrobial infections and the inflammatory component associated with some infections. Sertaconazole is currently approved as a 2% cream formulation in the United States for tinea pedis; however, dermatologic and gynecologic formulations exist, and sertaconazole has been used extensively in Europe for the treatment of superficial mycoses in both the dermatology and the gynecology disciplines. Sertaconazole has demonstrated efficacy, safety, and tolerability that are either similar or greater than those of other commonly used antifungal agents and has been shown in some studies to be associated with faster resolution of symptoms and a lower incidence of relapse. These attributes could likely lead to greater patient acceptance of and adherence to therapy beyond the eradication of fungal organisms. The potential for new uses of sertaconazole in other cutaneous and mucosal infections will continue to be investigated.

Table 4. Patients Treated With Sertaconazole for Intertrigo

| Location of intertrigo | Number of patients | Sex | Age, y | Cleared | Side effects? |
|------------------------|--------------------|--------|--------------|---------|---|
| Toe web | 4 | Male | 26-79 | Yes | One report of mild stinging and burning but did not discontinue |
| Groin | 1 | Female | 65 | Yes | No |
| Umbilicus | 1 | Female | 54 | Yes | No |
| Axilla | 1 | Male | 58 | Yes | No |
| Axilla | 1 | Female | 85 | Yes | Report of mild stinging and burning, but did not discontinue |
| Inframammary | 2 | Female | Not recorded | No | No |

Adapted with permission from Collier CN, Cantrell WC, Elewski BE. Poster presented at: 65th Annual Meeting of the American Academy of Dermatology; February 2-6, 2007; Washington, DC.

Release Date of Activity: May 2007 • Expiration Date of Activity for AMA PRA Credit: May 31, 2008

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CME INSTRUCTIONS

For each question or incomplete statement, choose the answer or completion that is correct. Circle the most appropriate response. Four of six responses are required for credit.

- The imidazole class of antifungals demonstrates marked variation in activity against which of the following organism groups?
 - Dermatophytes and *Malassezia furfur*
 - Dermatophytes, *Candida* species, and *M. furfur*
 - Dermatophytes and *Candida* species
 - Dermatophytes
- The absorption characteristics of sertaconazole may have which of the following clinical benefits?
 - Increased patient compliance
 - Need for less frequent application
 - Potential for maintenance therapy
 - All of the above
 - Both b and c
- Which of the following antifungal agents is (are) effective against the vaginal isolate *Gardnerella*?
 - Sertaconazole
 - Clotrimazole
 - Fluconazole
 - Both a and b
- Which of the following statements is not true?
 - Monotherapy with an antifungal agent is effective in the initial stages of athlete's foot.
 - The increasing severity of interdigital athlete's foot is characterized by an increase in fungi and a corresponding decrease in bacteria.
 - The increasing severity of interdigital athlete's foot is characterized by a decrease in fungi and a corresponding increase in bacteria.
- In which of the following indications has sertaconazole not demonstrated efficacy?
 - Tinea corporis
 - Mild to moderate psoriasis
 - Pityriasis versicolor
 - Seborrheic dermatitis
- Generic substitution may impact therapeutic outcomes in which of the following ways?
 - Changes in vehicle composition could lead to decreased patient tolerability.
 - Lack of equivalence between the generic and brand-name vehicle could impact penetration and absorption of the active drug into the skin.
 - Insufficient therapeutic response could be interpreted as drug inefficacy rather than a bioequivalence or formulation issue.
 - All of the above

COURSE EVALUATION

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PRETEST ASSESSMENT: Please rate your prior knowledge of azole antifungal agents on a scale of 1 to 5, with 1 being the lowest and 5 the highest. 1 2 3 4 5

COURSE EVALUATION: Please evaluate the effectiveness of this activity by circling your choice on a scale of 1 to 5, with 1 being the lowest and 5 the highest.

Objective #1: List the groups of organisms against which azole antifungals are active and realize the breadth of sertaconazole's activity against various organisms involved in superficial fungal infections 1 2 3 4 5

Objective #2: Understand how the absorption characteristics of sertaconazole could translate into therapeutic benefit 1 2 3 4 5

Objective #3: Describe sertaconazole's dual mechanism of action and what makes it unique among azole antifungals 1 2 3 4 5

Objective #4: Recognize the role of bacterial colonization in some fungal infections such as tinea pedis and intertrigo 1 2 3 4 5

Objective #5: Discuss the in vitro and in vivo anti-inflammatory effects of sertaconazole 1 2 3 4 5

Objective #6: Appreciate sertaconazole's clinical efficacy and safety in gynecologic conditions and dermatologic conditions other than tinea pedis 1 2 3 4 5

1. How do you rate the overall quality of the activity? 1 2 3 4 5

2. How do you rate the educational content of the activity? 1 2 3 4 5

3. After participation in this activity, have you decided to change one or more aspects in the treatment of your patients? _____ Yes _____ No

If yes, what change(s) will you make?

If no, why not?

4. Was the presented information fair, objective, balanced, and free of bias in the discussion of any commercial product or service? _____ Yes _____ No

If no, please comment:

5. Suggested topics for future activities:

6. Suggested authors for future activities:

7. Would you be willing to participate in postactivity follow-up surveys? _____ Yes _____ No

8. Would you be willing to participate in a phone, e-mail, or in-person discussion exploring ways to improve our CME activities? _____ Yes _____ No

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