Sertaconazole Nitrate Cream 2% for the Treatment of Tinea Pedis

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Tinea pedis, both in its acute and chronic phase, is a common skin condition that often is overlooked but can lead to onychomycosis and acute bacterial cellulitis if left untreated. Therefore, aggressive treatment with a topical antifungal agent is warranted. Sertaconazole nitrate cream 2% is a newer imidazole agent that possesses both fungicidal and fungistatic properties to eradicate existing infections. In addition to antifungal properties, it exhibits anti-inflammatory and antipruritic effects. Controlled clinical trials have confirmed its safety, tolerability, and efficacy in participants with tinea pedis. We report 2 patients with chronic tinea pedis of many years' duration and demonstrate the usefulness of sertaconazole nitrate cream 2% in the clinical setting. Tinea pedis was confirmed by results of a potassium hydroxide preparation. Both patients experienced marked improvement by the second week of twice-daily treatment with sertaconazole nitrate cream 2%. Clinical cure was achieved in both patients. These findings suggest that sertaconazole nitrate cream 2% is an effective option for the treatment of tinea pedis.

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As recently as a century ago, tinea pedis was an uncommon clinical finding.[1] Today, it is the most common dermatophyte host worldwide. Although tinea pedis is associated with various complications, one of the most frequent being onychomycosis, it often is overlooked by medical professionals.[1] It is well-established that *Trichophyton rubrum* is the predominant causative agent of tinea pedis as well as onychomycosis. According to the results of an epidemiologic surveillance study conducted in the United States, the incidence of tinea pedis infections caused by *T rubrum* has steadily risen from 57% in 1999 to 83% in 2002. *Trichophyton rubrum* also was found to be the predominant causative agent of onychomycosis, with the incidence of positive cultures increasing from 55% in 1999 to 73% in 2002.[2]

A growing body of data indicates that there is a strong correlation between the presence of tinea pedis and onychomycosis. In one study, investigators retrospectively reviewed the results of toenail clippings examined histologically with periodic acid–Schiff staining submitted over 5 years. The presence of tinea pedis was significantly correlated with a histologic diagnosis of onychomycosis ($P<.001$).[3]

Tinea pedis is considered a precursor to onychomycosis.[4] It appears that certain individuals are genetically predisposed to develop *T rubrum* infections based on an autosomal dominant inheritance pattern and an infection that initially begins as tinea pedis can be transferred or extended to other body sites, such as the nails.[5] Specifically, the fungus invades the horny layer of the hyponychium and/or the nail bed, then the undersurface of the nail plate. Afterward, the disease spreads proximally.[6] Once the nails are infected, they become reservoirs for continued infection of the surrounding skin, resulting in what can best be described as a continuum of reinfection.[4]

Appropriate diagnosis and treatment are essential to break this cycle. Early treatment of tinea pedis may prevent progression to onychomycosis.

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Topical antifungal agents generally are considered first-line therapy for the treatment of tinea pedis because they usually are effective in eliminating dermal fungi without the need for systemic therapy[7] and with fewer associated adverse effects.[8]

Sertaconazole nitrate cream 2% is a newer imidazole agent that possesses both fungicidal and fungistatic properties to eradicate existing infections.[9] It has a broad spectrum of activity in vitro[10] and has been shown to be more active against *T rubrum* than fluconazole, isoconazole, ketoconazole, or miconazole, with the lowest number of resistant isolates.[11] After a single dose, drug concentrations are maintained beyond the minimum inhibitory concentration for 90% of species growth for up to 48 hours.[12] Sertaconazole nitrate cream 2% contains a highly lipophilic benzothiophene fragment that enhances penetration into the stratum corneum. Substantial levels of the drug are present in the skin within 30 minutes of application and 72% of the dose is still present 24 hours after administration of a single dose, suggesting a reservoir effect.[12]

Anti-inflammatory and Antipruritic Properties

Inflammation associated with the lesions of tinea pedis makes the infection more symptomatic. Inflammatory cytokines including tumor necrosis factor α (TNF-α), IL-2, interferon-γ (IFN-γ), IL-4, and granulocyte-macrophage colony-stimulating factor are stimulated by fungal infections.[13] These cytokines activate the inflammatory pathways that cause discomfort. Antifungal agents with anti-inflammatory properties are desirable because they reverse morbidity without affecting efficacy.[7] Sertaconazole nitrate has been shown to inhibit the release of the cytokines TNF-α, IL-2, IFN-γ, IL-4, and granulocyte-macrophage colony-stimulating factor from activated human lymphocytes.[13] Sertaconazole nitrate was significantly more potent against the release of all cytokines compared with the other antifungal agents tested (ie, butoconazole nitrate, ciclopirox olamine, fluconazole, miconazole, terconazole, tioconazole, ketoconazole)($P<.05$). Sertaconazole nitrate also reduced amounts of TNF-α, IL-2, and IFN-γ in inflamed murine tissue.[13] The cellular mechanism by which sertaconazole nitrate exerts its anti-inflammatory activity has been investigated in keratinocytes and peripheral blood mononuclear cells, and it has been determined that sertaconazole nitrate exhibits anti-inflammatory activity via the p38–cyclooxygenase 2–prostaglandin E_2 pathway.[14]

Sertaconazole nitrate also may inhibit the secondary inflammation induced by scratching and thus help prevent disruption of the skin barrier function.[13] Pruritus is one of the symptoms of tinea pedis and may lead to disruption of the skin barrier, allowing entry of foreign bacteria and potential for superinfection. In addition to its anti-inflammatory activities, sertaconazole nitrate demonstrates antipruritic activity. In an in vivo animal model, topical application of sertaconazole nitrate reduced substance P–induced itch.[13] The reduction in scratching in sertaconazole-treated animals was comparable to the reduction in scratching in hydrocortisone-treated animals. This anti-inflammatory and antipruritic activity may alleviate the need for corticosteroids in some patients and help break the itch-scratch cycle, thereby helping to prevent spread to other body sites.[13]

Safety and Tolerability

The safety and tolerability profile of sertaconazole nitrate cream 2% compares favorably with other agents in the topical imidazole class. In a report of 2 studies conducted in the United States with 588 participants, sertaconazole nitrate cream 2% was not associated with any serious adverse events and cutaneous adverse events were comparable between sertaconazole-treated and vehicle-treated groups.[15]

Clinical Efficacy

Sertaconazole nitrate cream 2% is indicated for the treatment of tinea pedis in immunocompetent patients 12 years and older. The efficacy of sertaconazole nitrate cream 2% has been confirmed in 2 randomized, multicenter, double-blind, parallel group, vehicle-controlled studies conducted in the United States in which participants (N=588) were randomized to treatment with sertaconazole or vehicle applied twice daily for 4 weeks.[15] Sertaconazole-treated participants had significantly higher rates of successful treatment outcomes, defined as either effective clinical treatment (mycologic cure in addition to marked improvement of clinical symptoms over baseline) or clinical cure (mycologic cure and normal appearance of the skin), versus vehicle-treated participants ($P<.0001$). Significant reductions in the signs and symptoms of erythema ($P<.0001$), pruritus ($P=.0001$), and scaling ($P=.0046$) were observed by investigators in participants treated with sertaconazole nitrate cream 2% compared to the vehicle group at week 4. The number of participants who reported relief from pruritus, a secondary efficacy measure, increased from 20% at baseline to 77% after only 1 week of therapy with sertaconazole nitrate cream 2%.[15]

The following case reports demonstrate the use of sertaconazole nitrate cream 2% in patients with tinea pedis as well as concomitant onychomycosis or a history of onychomycosis, a situation that frequently presents in clinical practice.

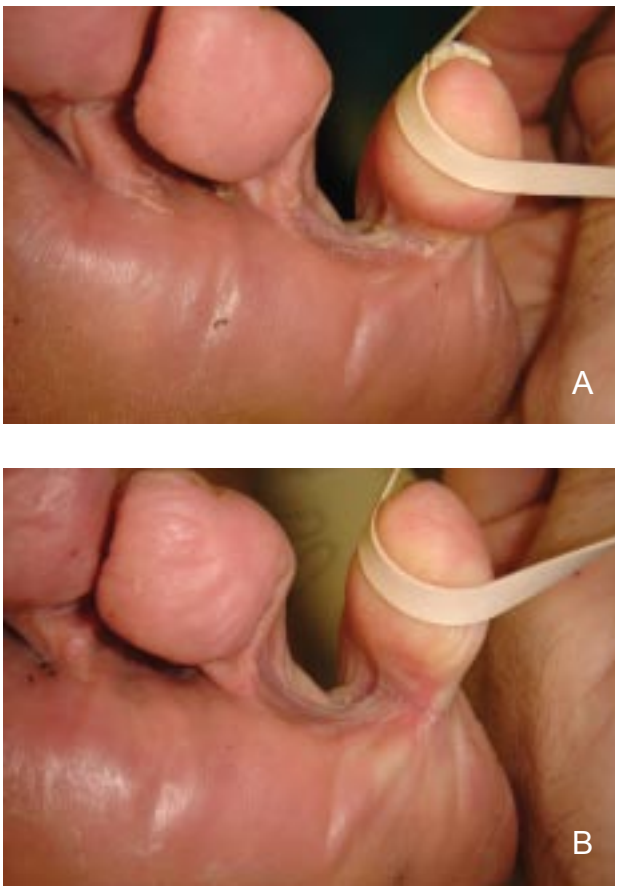

Figure 1. Initial examination of a 72-year-old man revealed positive signs of tinea pedis on the dorsal aspects of the feet, including moderate scaling, hyperkeratosis, mild fissures, and interdigital maceration (A). After 2 weeks of twice-daily treatment with sertaconazole nitrate cream 2%, there were no signs of fissures, interdigital maceration, erythema, or vesiculation, and only mild scaling and hyperkeratosis were noted (B).

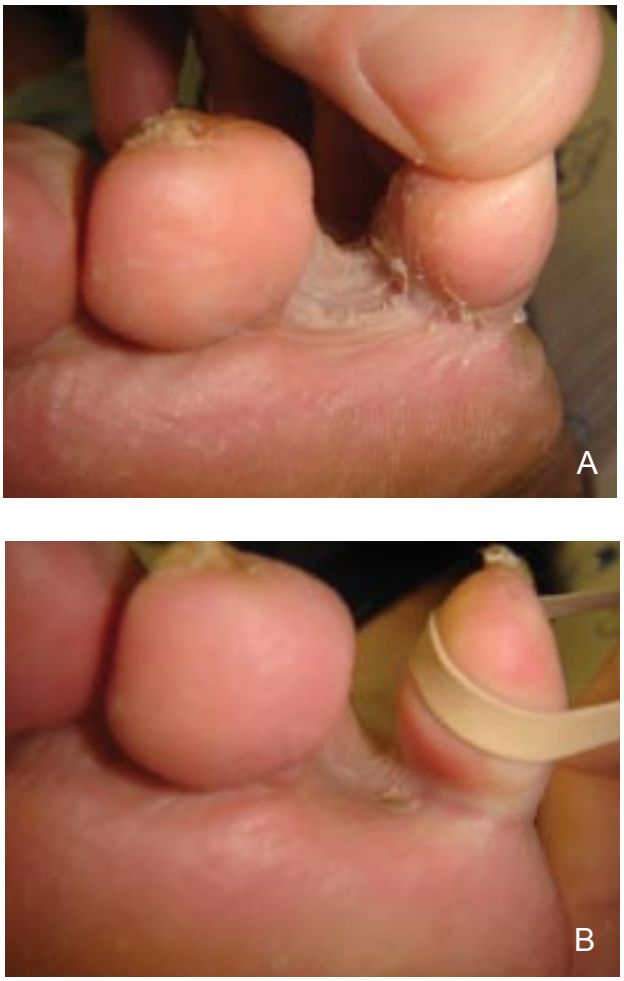

Figure 2. Initial examination of a 68-year-old woman revealed positive signs of tinea pedis, including moderate scaling and hyperkeratosis, as well as mild erythema, fissures, and interdigital maceration (A). After 4 weeks of twice-daily treatment with sertaconazole nitrate cream 2%, a reduction in the presence of fissures and improvement in interdigital maceration were noted (B).

Case Reports

Patient 1—A 72-year-old man presented with tinea pedis and onychomycosis. He had previously undergone a prostatectomy, coronary artery bypass surgery, and aortic valve replacement, and was being treated with metoprolol succinate, misoprostol, extended-release potassium chloride, and ranitidine hydrochloride. He reported no medical history of diabetes mellitus, asthma, ulcers, rheumatic fever, phlebitis, stroke, hepatitis, or thyroid disease. Gross examination of the feet revealed turgor, texture, and elasticity, with multiple actinic keratoses on the dorsal aspects. Positive signs of tinea pedis were observed on the dorsal aspects of the feet, including moderate scaling and hyperkeratosis as well as mild fissures and interdigital maceration (Figure 1A); however, there was no erythema or vesiculation. The patient reported moderate scaling, mild itching, and odor, but no redness, pain, or burning. A potassium hydroxide preparation of a skin sample at the initial evaluation revealed the presence of fungal elements. The patient was instructed to apply sertaconazole nitrate cream 2% to the feet twice daily and was clinically followed over 8 weeks. By the second visit at week 2, there were no signs of fissures, interdigital maceration, erythema, or vesiculation, and only mild scaling and hyperkeratosis were noted (Figure 1B). The patient reported an improvement in itching and odor. Physician-observed signs of infection and patient-reported symptoms showed improvement throughout the remaining 6 weeks of treatment. No irritation or other adverse effects were associated with treatment.

Patient 2—A 68-year-old woman presented with tinea pedis and a history of onychomycosis. Positive signs of tinea pedis included moderate scaling and hyperkeratosis, as well as mild erythema, fissures, and interdigital maceration (Figure 2A). At the initial visit, the patient reported moderate scaling, mild pain, and burning. A potassium hydroxide preparation of a skin sample revealed the presence of fungal elements. The patient had a history of diabetes mellitus, neuropathy, peripheral vascular disease, and mitral valve prolapse, and was being treated with insulin and valsartan. After 2 weeks of therapy with sertaconazole nitrate cream 2% applied to the feet twice daily, there was no erythema, improvement in scaling was observed by the physician and patient, and the patient reported a reduction of pain and burning. After 4 weeks of treatment, a reduction in the presence of fissures and improvement in interdigital maceration were noted (Figure 2B).

Comment

Tinea pedis is a common but potentially serious fungal infection that often is a precursor to onychomycosis. Once the nails are infected, they become reservoirs for continued infection of the surrounding skin, potentially resulting in a cycle of reinfection.[4] Tinea pedis has been shown to be a significant risk factor for acute bacterial cellulitis ($P<.001$).[16] When not properly treated, it may be a risk factor for increased complications in patients with diabetes mellitus or peripheral vascular disease.[1] As a result, effective antifungal treatment is essential to achieve a favorable clinical and mycologic outcome in patients with tinea pedis. In addition to antifungal activity, sertaconazole nitrate exhibits anti-inflammatory and antipruritic properties, which may help relieve the symptoms of infection. Clinical trials have confirmed the safety and efficacy of sertaconazole nitrate cream 2% in the treatment of tinea pedis.[15] Consistent with the results of the clinical trials, the 2 patients reported here responded favorably to treatment and were considered markedly improved within 2 weeks of initiating treatment. Sertaconazole nitrate cream 2% was well-tolerated and no adverse effects were reported.

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