Significant Absorption of Topical Tacrolimus in 3 Patients With Netherton Syndrome

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Background: Tacrolimus is a macrolide immunosuppressant approved in oral and intravenous formulations for primary immunosuppression in liver and kidney transplantation. Topical 0.1% tacrolimus ointment has recently been shown to be effective in atopic dermatitis for children as young as 2 years of age, with minimal systemic absorption. We describe 3 patients treated with topical 0.1% tacrolimus who developed significant systemic absorption.

Observation: Three patients previously diagnosed as having Netherton syndrome were treated at different centers with 0.1% tacrolimus ointment twice daily. Two patients showed dramatic improvement. All patients were found to have tacrolimus blood levels within or above the established therapeutic trough range for oral tacrolimus in organ transplant recipients. None of these patients developed signs or symptoms of toxic effects of tacrolimus.

Conclusions: Patients with Netherton syndrome have a skin barrier dysfunction that puts them at risk for increased percutaneous absorption. The Food and Drug Administration recently approved 0.1% tacrolimus ointment for the treatment of atopic dermatitis. Children with Netherton syndrome may be misdiagnosed as having atopic dermatitis. These children are at risk for marked systemic absorption and associated toxic effects. If topical tacrolimus is used in this setting, monitoring of serum tacrolimus levels is essential.

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Netherton Syndrome is an autosomal recessive disorder characterized by congenital erythroderma, hair shaft defects, frequent infections, poor growth, and food allergies. The gene defect was recently localized to chromosome 5q32 and identified as a mutation in the SPINK5 gene, encoding the serine protease inhibitor LEKTI (lymphoepithelial Kazal-type related inhibitor).

The pathognomonic cutaneous finding in Netherton syndrome, ichthyosis linearis circumflexa, develops in 75% of cases but is not usually evident in infancy or early childhood. A more common presenting sign is generalized redness and scaling, which has been mistaken for atopic dermatitis. The erythroderma is often widespread and resistant to therapy. A recent report described a 20-year-old man with ichthyosis linearis circumflexa who improved dramatically with topical tacrolimus treatment. We describe 3 children with Netherton syndrome and erythroderma treated with 0.1% tacrolimus ointment who experienced significant percutaneous absorption of the drug, with serum levels well above the therapeutic range.

Report of Cases

Case 1

A 5-year-old boy had been born prematurely and had had congenital erythroderma complicated by Staphylococcus aureus sepsis. Continuing problems beyond the neonatal period included erythroderma with scaling scalp, sparse hair, frequent otitis media, recurrent sinusitis, and poor growth. Netherton syndrome was diagnosed at 9 months of age by demonstration of the pathognomonic hair shaft defect, trichorrhexis invaginata. Initially, his skin care regimen consisted of daily bathing with Cetaphil (Galderma Laboratories, LP, Paris, France) and frequent use of Aquaphor (Beiersdorf Inc, Wilton, Conn). He was unavailable for follow-up care from ages 3 to 5 years.

At age 5 years, his erythroderma was unresponsive to conservative topical therapies, including ketoconazole shampoo and 2.5% tar ointment, as well as more aggres-
sive short trials with limited applications of lactic and salicylic acid lotion and 0.1% tazarotene ointment alone and in combination with a class 1 topical corticosteroid. Aggressive treatments were used on limited areas for a maximum of 1 week because of concern about percutaneous absorption. We treated this patient in a double-blinded fashion with extemporaneously formulated 0.1% tacrolimus in white petrolatum twice daily on one side of the scalp and face and white petrolatum on the other side. He had a marked decrease in crusting, scale, and erythema on both sides, but the tacrolimus-treated side was noted at 3-week and 8-week follow-up visits to have near-complete clearing. A total of 15 g of tacrolimus ointment was then applied sparingly to his trunk, shoulders, scalp, and face twice daily. On day 5, whole-blood tacrolimus level was 37.2 ng/mL 2 hours after treatment (therapeutic trough range in organ transplant recipients, 5-20 ng/mL). Care was taken to draw the blood from a site that had not been treated for 2 days before the phlebotomy. One week later, a second 2-hour postdose drug level was 19 ng/mL with the patient receiving the same dose of medication. Despite these levels, his blood pressure, serum electrolyte levels, glucose level, complete blood cell count, serum urea nitrogen level, and serum creatinine level remained within normal limits. Subsequently, the drug was applied twice a week, only to the most severely involved areas, the scalp and face. On this regimen, postapplication blood levels monitored at 2-day trough times were less than 1.5 ng/mL (lower limit of quantitation for the assay).

CASE 2

A 14-year-old girl presented with trichorrhexis invaginata, short stature, patches of ichthyosis linearis circumflexa, and widespread congenital erythroderma associated with severe pruritus and elevated IgE level. Her dermatitis and pruritus had been treated long-term with applications of 0.1% triamcinolone acetonide ointment since early infancy. During the preceding 5 years, her course had been complicated by recurrent staphylococcal and streptococcal skin infections, flares of her erythroderma, and poor growth, falling below the fifth percentile for age. At chronological age 10 years 5 months, her bone age was 6 years 10 months, which was delayed 2 SDs below the mean. Adrenocortical suppression was documented, with a low morning cortisol level of 13.8 nmol/L (reference range, > 118.6 nmol/L). She was subsequently given a lower-potency topical corticosteroid (fluocinolone oil [Derma-smoothe FS; Hill Dermaceuticals, Inc, Sanford, Fla]) and growth hormone replacement, resulting in a 6-cm growth spurt during 9 months.

At age 12 years, she was treated with extemporaneously compounded 0.1% tacrolimus ointment applied to one leg twice a day for 1 month, resulting in marked improvement. For the next 6 months, she applied the compounded ointment to a larger area, with excellent response. Blood levels were not monitored. Two months later, she was enrolled in an open-label study of 0.1% tacrolimus ointment for the treatment of atopic dermatitis (Fujisawa Healthcare, Inc, Deerfield, Ill; protocol 99-0-054). Three applications of study drug caused intolerable stinging and exudative erythroderma, which subsided after 1 week without the medication. Results of patch tests with the study drug and the extemporaneous compound ointment were negative. Another trial of proprietary 0.1% tacrolimus ointment was applied to one arm twice a day for 7 days, with the same adverse reaction. A tacrolimus level determined within 48 hours of the last application was 23 ng/mL. Complete blood cell count, renal function, and hepatic function were normal. The patient did not tolerate retreatment with extemporaneously compounded 0.03% tacrolimus ointment. A 24-hour postapplication drug level was 8.3 ng/mL. She elected to discontinue treatment with tacrolimus ointment.

CASE 3

A 3-year-old boy had been born with facial erythema and a scaly patch on his left wrist. During the first week of life, he had developed more widespread erythematous, polycyclic, and serpiginous plaques with migratory, hyperkeratotic, double-edged peripheral scaling. At birth, he had had long dark hair, which fell out after a few weeks and was replaced by sparse, brittle hair. Infantile and childhood had been complicated by frequent otitis media and externa; allergies to spinach, peanuts, milk, and eggs; and erythroderma. The patient was only minimally responsive to numerous topical corticosteroid preparations and antihistamines. The diagnosis of Netherton syndrome had been confirmed at age 2 years, when trichorrhexis invaginata was found on light microscopic examination of the patient’s hair.

At age 3 years, the patient was deemed eligible for inclusion in a clinical trial of 0.1% tacrolimus ointment twice daily for the treatment of atopic dermatitis (Fujisawa Healthcare, Inc, protocol 99-0-054). The protocol did not include monitoring of laboratory measures. An average of 3 g was spread over the body and scalp with each application. Baseline and follow-up blood pressures remained within normal limits (measured with an age-appropriate cuff, 80/50 mm Hg at baseline and 90/55 mm Hg at his 6-month visit). The patient experienced rapid improvement in his skin along with decreased pruritus and slow regrowth of his hair. After 8 months of intermittent therapy (interrupted by two 2-week courses of systemic corticosteroids), a blood level was obtained to monitor for systemic absorption. The level, 10.2 ng/mL, was determined 30 hours after the last application of medication from a site that had not been treated for 2 days before phlebotomy. Complete blood cell count, renal function, and hepatic function were normal. The patient’s parents elected to discontinue use.

Despite dramatic clinical improvement with topical tacrolimus in these 3 cases, the risk of systemic exposure from percutaneous absorption is a serious concern in Netherton syndrome. At 11 hours after dosing, the therapeutic trough range for oral tacrolimus (Prograf; Fujisawa Healthcare, Inc) in organ transplant recipients has been defined at 5 to 20 ng/mL. The pharmacokinetics of topically applied tacrolimus have been less well de-
Rex and colleagues have described an ominous long-term complication. They observed that the signs and symptoms of tacrolimus exposure to high blood levels of drug were brief in cases 1 and 2. The signs and symptoms of tacrolimus toxic effects were consistent with the pathogenic sequence illustrated in the Figure. Premature activation of the stratum corneum tryptic enzyme would result in activation of phospholipase A₂. This could then stimulate premature lamellar body secretion, a unique ultrastructural finding in Netherton syndrome, as well as disruption of the plasma membrane, triggering cytolysis or premature cornification. At the same time, unchecked activation of the stratum corneum tryptic enzyme would lead to premature degradation of corneodesmosomes, as well as premature desquamation and thinning of the stratum corneum. Both of these actions would result in a defective permeability barrier and could account for the increased absorption and high blood levels of tacrolimus in these cases of Netherton syndrome. Finally, serine proteases may also be involved in releasing stratum corneum interleukin 1 from its inactive form, which could lead to the marked inflammation characteristic of Netherton syndrome. Interruption of this inflammatory sequence may account for the beneficial effects of topical anti-inflammatory drugs, such as tacrolimus, in this disorder.

Clinical experience with topical tacrolimus has been limited to investigational trials in patients older than 2 years with atopic dermatitis. In a well-controlled study of pediatric patients, 2 to 15 years of age, with moderate and severe atopic dermatitis, mean and median blood levels were below the limit of quantitation. Tacrolimus blood levels in the therapeutic transplant trough range were not detected in any subject. Quantifiable blood levels invariably occurred during the first week of therapy and diminished as patients' skin disease improved. Infants and young children with widespread areas of active disease are at highest risk for significant percutaneous absorption of the drug.

On December 8, 2000, tacrolimus ointment (Protopic; Fujisawa Healthcare, Inc) received approval by the US Food and Drug Administration for the treatment of atopic dermatitis in children as young as 2 years. Before marketing, an extemporaneously compounded form of the drug had been prescribed in accordance with a published formula that use tacrolimus capsules. With commercial availability, tacrolimus ointment will likely become the treatment of choice for children with severe or corticosteroid-dependent atopic dermatitis. Because children with Netherton syndrome are often either misdiagnosed as having only atopic dermatitis or assumed to have atopic dermatitis in association with Netherton syndrome, as in our cases 2 and 3, it will be important to identify these children correctly before topical tacrolimus therapy is initiated. Sparse or brittle hair, frequent infections, and poor growth in an erythrodermic child should prompt appropriate investigation for Netherton syndrome. The risk of cutaneous tacrolimus–associated cutaneous B-cell lym-
phoproliferative disease can be appreciated only after long-term use in a large patient population. Special caution must be taken with regard to this potential adverse effect when topical tacrolimus is prescribed for patients with a primary immunodeficiency such as Netherton syndrome. We also believe that the potential risk of marked systemic absorption with associated acute toxic effects must be considered in any child with extensive skin disease, or any infant, regardless of the extent of disease, because of their high ratio of body surface area to weight. If topical tacrolimus ointment is prescribed in any of these settings, close monitoring with plasma drug levels is essential.

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REFERENCES