

Allergic contact dermatitis caused by calcipotriol

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Summary

Background. Calcipotriol, a synthetic vitamin D analogue, is widely used for the topical treatment of psoriasis. It often causes irritant reactions, whereas allergic contact dermatitis has less commonly been reported.

Objectives. To report on 6 patients (among them an 11-year-old child) who presented with eczematous lesions complicating pre-existing dermatitis, observed in our tertiary referral patch test clinic between 2004 and 2016.

Methods. Patch tests were performed with the commercial preparation used by the patients and/or its ingredients, including calcipotriol (2 or 10 µg/ml in isopropyl alcohol), according to ESCD patch test guidelines.

Results. Allergic contact dermatitis was confirmed in all cases, and the lesions improved following treatment with topical corticosteroids and/or oral medication.

Conclusions. When topical treatment with calcipotriol fails to improve, or even worsens, existing skin lesions, contact allergy should be suspected. A patch test concentration of 2 µg/ml in isopropyl alcohol seems to be the most suitable. According to the literature, patients sensitized to calcipotriol may tolerate topical therapy with other vitamin D3 analogues, particularly tacalcitol.

Key words: allergic contact dermatitis; calcipotriol; CAS no. 112828-00-9; contact allergy; psoriasis; sensitization; topical drugs; vitamin D3 derivative.

Vitamin D analogues, such as calcipotriol, are widely used for the topical treatment of psoriasis, given their normalizing effect on the hyperproliferation and abnormal differentiation of keratinocytes, as well their immunomodulatory effects (1). Immunosuppressive effects are mediated through modulation of the production of cytokines by keratinocytes, and decreased antigen presentation and suppression of the ability to stimulate

T cell proliferation by Langerhans cells (2, 3). However, their potential to induce skin irritancy (4), which represents a 'danger signal', may predispose to skin sensitization (5) and thus allergic contact dermatitis, as has occasionally been described (6–15). Six patients, 2 men and 4 women, suffering from allergic contact dermatitis caused by calcipotriol observed in our tertiary patch test clinic between 2004 and 2016, are presented here.

Methods

Patch tests were performed with the commercial preparations in cases 2, 4, and 6, and/or their ingredients, including calcipotriol (2 µg/ml and in case 1 also 10 µg/ml in isopropyl alcohol, as kindly provided by the respective company). IQ Ultra[®] Chambers (Chemotechnique Diagnostics, Vellinge, Sweden) were used, and readings were scored according to the ESCD patch testing guideline (16). Unfortunately, the solvent isopropyl alcohol was tested only in case 5.

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Table 1. Patch test results

Patient	Lesion location	Patch test with calcipotriol 2 µg/ml	Patch test with calcipotriol 10 µg/ml	Commercial preparation used, patch test result	Other positive patch test reactions
1. F, 49 years	Feet	D2 +, D4 ++	D2 +, D4 ++	Daivonex® cream, NT	Colophonium (D2 +, D4 ++) Adhesive tapes (D2 +, D4 +)
2. F, 59 years	Scalp	D2 ?+, D4 +	NT	Daivonex® lotion, D2 +, D4 +	–
3. F, 50 years	Feet	D2 +, D4 ++	NT	Daivonex® ointment, NT	Potassium dichromate (D2 ?, D4 +) <i>Myroxylon pereirae</i> (D2 +, D4 ++) Thiuram mix (D2 ?, D4 +)
4. M, 26 years	Hands and feet	D2 –, D4 +	NT	Daivonex® cream, D2 NR, D4 ++	Colophonium (D2 –, D4 +)
5. F, 10 years	Hands	D2 –, D4 +	NT	Daivonex® cream, NT	–
6. M, 32 years	Hands and feet	D2 +, D4 +	NT	Dovobet® ointment, D2 +, D4 +	–

F, female patient; M, male patient; D, day; NT, not tested; NR, not read.

Results

Case 1

A 49-year-old non-atopic woman consulted us in August 2004 because of an itching erythematous-squamous dermatitis of both soles of 3-year duration. She had been treated with local PUVA, topical corticosteroids, camomile cream, and Daivonex® cream (LEO Pharma, Ballerup, Denmark), the last of which had worsened the symptoms. She also reported being allergic to nickel. Patch testing was performed with the baseline series, a water-resistant adhesive, and an adhesive tape that she had applied. Positive reactions were observed to colophonium, to both of the adhesives, and to calcipotriol (Table 1), all considered to be relevant for her dermatitis.

Case 2

This 59-year-old woman, who was suffering from psoriasis capitis for which she sporadically applied Daivonex® lotion, was referred to us by her dermatologist in March 2005 because of suspected allergic contact dermatitis caused by hair dyes, as she had experienced itching after using these. Application of Daivonex® lotion to the scalp had been followed by the appearance of acute weeping eczema on the following day. Previous patch testing had already shown positive reactions to both the hair dyes and the lotion. Additional testing with the baseline and a hairdresser series (Chemotechnique Diagnostics) showed positive reactions to the lotion and to calcipotriol (Table 1), both of which were relevant for the acute dermatitis on her scalp.

Case 3

A 50-year-old woman consulted us in March 2005 because of a skin eruption localized on the arms, upper legs, and hands, which had appeared 2 weeks previously,

and for which she used topical corticosteroids; for several months, she had also been suffering from eczematous lesions on both feet, to which she had applied Daivonex® ointment. She was a bank clerk, and also performed household work, during which she used rubber gloves. Patch testing with the baseline series, a shoe series, and a textile series, as well as some of the products used, along with the ingredients, showed positive reactions to potassium dichromate, *Myroxylon pereirae*, thiuram mix, and calcipotriol (Table 1). The results were considered to be relevant: shoe dermatitis caused by chromium, and *M. pereirae* present in a topical cream she had applied, thiuram mix in the rubber household gloves used due to hand dermatitis, and calcipotriol ointment having worsened her foot dermatitis.

Case 4

A 26-year-old man had consulted us for several years because of palmoplantar psoriasis and atopic dermatitis (besides hay fever and asthma). Moreover, previous patch testing by his dermatologist had shown multiple positive reactions to colophonium, wool alcohols, diaminodiphenyl methane, the patient's own shoes, and Daivonex® cream. In 2008, patch testing was again performed with the baseline series and a shoe series, and the ingredients of the latter preparation. The patient reacted positively to calcipotriol (Table 1), which was relevant for his secondary allergic contact dermatitis.

Case 5

A 10-year-old atopic girl with eczema and hay fever was referred to our general outpatient clinic in January 2009 because of severe dermatitis on the hands (Fig. 1). She had suffered for 5 years, and particularly during winter, from itching, which was sometimes burning and painful, and vesicular and bullous lesions on both palms, and,



Fig. 1. Illustration of a 10-year old girl with severe dermatitis on the hands and a positive patch test reaction to calcipotriol 2 µg/ml in isopropyl alcohol, read on day 4.

until 2008, also on the soles of the feet, for which multiple treatments had been administered. These included topical corticosteroids, antiseptics, and Daivonex[®] cream. Other body sites had never been affected. A chronic childhood bullous disease, that is, linear IgA dermatosis, could be excluded based on a skin biopsy. Moreover, an atypical presentation of pustular psoriasis, dyshidrotic eczema and allergic contact dermatitis were considered as differential diagnoses. Hence, patch tests were performed in February with the baseline series, the topical products used, and calcipotriol, which was the only allergen yielding a positive reaction (Table 1). In March of that year, the patient consulted again because of severe bullous lesions, for which both a local corticosteroid and antiseptic cream, and oral antibiotics, were administered. The diagnosis of severe dyshidrosis with superinfection (*Staphylococcus aureus*) was made. Unfortunately, the patient did not attend for further follow-up.

Case 6

A 32-year-old atopic man, who worked as an administrator and who had contact with glues and cement in his leisure time, consulted us in 2011 because of an itching dermatitis with erythema, scaling, pustules and fissures on both palms and soles of 1-year duration. Moreover, he had also suffered from eczematous lesions on the backs of the feet and in his body folds, which had been diagnosed as atopic dermatitis. Several treatments had been administered, including PUVA therapy, topical corticosteroids and antiseptics, Dovobet[®] ointment (containing both calcipotriol and betamethasone dipropionate; LEO Pharma), oral antibiotics, cyclosporine, and antimycotics. Patch testing with the baseline series, a shoe series, and the topical products used, along with the ingredients, showed reactions only to Dovobet[®], tested 'as is', and calcipotriol (Table 1), which were relevant for the persisting dermatitis 'despite treatment', complicating the patient's pre-existing psoriatic lesions.

Discussion

Although contact allergy to calcipotriol and analogues seems to be rare in relation to their widespread use, a few cases have been previously reported in the literature (6–15). Hence, when topical treatment with calcipotriol fails to improve, or even worsens, the existing lesions, contact allergy should be ruled out. Given its irritant potential, patch testing with the ointment 'as is' may remain non-conclusive (6); on the basis of previous studies (7), cases of suspected allergy should therefore be patch tested with 2 µg/ml calcipotriol in citrate-buffered isopropanol solution. Our patients were patch tested with this dilution, and, in 1 case, also with 10 µg/ml in isopropyl alcohol. Positive patch test reactions were obtained in all 6 patients, and, as the lesions improved following replacement of calcipotriol therapy with topical corticosteroids and/or oral medication, we could confirm the diagnosis of allergic contact dermatitis in them.

According to the literature, testing at different concentrations between 2 and 10 µg/ml may be helpful to differentiate between allergic and irritant reactions (4), whereas another study reported on patch testing with serial dilutions down to 0.08 µg/ml (6). Furthermore, a repeated open application test (ROAT) with the commercial preparation seems to be valuable. In the study reported by Frosch et al. (6), a ROAT with Psorcutan[®] ointment (LEO Pharma) applied twice daily for 14 days gave only faint and transient erythema in 2 of 15 healthy controls. Interestingly, Zollner et al. were able to confirm their positive patch test result with a positive lymphocyte proliferation test result (12). According to the latter,

patients sensitized to calcipotriol may tolerate topical therapy with tacalcitol, which was later confirmed by other authors (6, 13). Kimura et al. reported a patient with contact allergy to tacalcitol and cross-reactivity with calcitriol, the biologically active form of vitamin D, which is only used orally in Belgium to treat hypoparathyroidism and renal osteodystrophy (14). Bruynzeel et al. published a case of allergic contact dermatitis caused by calcipotriol with cross-reactivity to 25-hydroxyvitamin

D3 and 1- α -hydroxyvitamin D3, but not to calcitriol and ergocalciferol (15). Consequently, cross-reactivity should always be checked for; unfortunately, we could not do this in our cases.

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