

Contact allergy to calcipotriol does exist

Report of an unequivocal case and review of the literature

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A 64-year-old woman developed an itchy papulovesicular dermatitis at the periphery of psoriatic plaques on the lower legs after the daily application of calcipotriol ointment (Psorcutan® Salbe) for 2 weeks. She had used the same ointment for 4 weeks 6 months before. Patch testing revealed strongly positive reactions to the marketed product and to the active ingredient calcipotriol in a concentration series (2.0, 10.0 and 50.0 µg/ml in isopropyl alcohol). A repeated open application test (ROAT) on the forearms showed a vesicular dermatitis after 4 days on the side that received the calcipotriol ointment, whereas the control with the placebo ointment remained completely negative. Histologic examination of the ++ patch test reaction was in line with the picture of contact allergy. Retesting after 6 months confirmed the hypersensitivity, with a positive reaction even at 0.4 µg/ml. For comparison, the ROAT with calcipotriol ointment was performed for 2 weeks on both forearms of 15 volunteers never exposed to calcipotriol before. Only 2 subjects developed a slight reaction on days 5 and 11, respectively. Based on this case and on previous reports in the literature, calcipotriol must now be regarded as both a contact allergen and an irritant. For patch testing, a concentration of 2 µg/ml in isopropyl alcohol is the most suitable. If the reaction is only weakly positive and not reproducible after some time, it might be of the irritant type. In unclear cases, a ROAT should be performed. A severe papulovesicular dermatitis within 1 week will confirm the presence of contact allergy.

Key words: calcipotriol; contact allergy; ROAT; psoriasis; medicaments; patch testing technique.
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Calcipotriol is now widely used for topical treatment of psoriasis. The manufacturer (Leo Pharmaceutical Products, Ballerup, Denmark) and the distributor in Germany (Schering AG, Berlin) emphasize the possibility of *irritation*, particularly in intertriginous areas ("pruritus, burning and erythema"). According to the German special drug information for dermatologists, "irritation may be more intense in rare cases and may show pustules, papules or blisters" (Fachinformation für Psorcutan, August 1995). Contact allergy as a possible adverse effect is not mentioned. In this report, we present a typical case of contact allergy to calcipotriol. Together with a critical review of the literature, there is now sufficient evidence to classify calcipotriol not only as an irritant but also as a contact sensitizer.

Case Report

A 64-year-old woman had had psoriasis for 10 years. She had had no serious diseases in the past

and was free of atopic symptoms. In February 1997, she was started on treatment with calcipotriol ointment (Psorcutan® Salbe) for large psoriatic plaques on both lower legs and smaller lesions on the elbows, chest and sacral region. After 2 weeks of 2 × daily applications, some improvement was noted, but there was marked irritation and burning in the pretibial and sacral locations. The frequency of applications was reduced to 1 × daily and a potent corticosteroid was prescribed in addition. Under this regimen, all lesions cleared within 4 weeks. In August, while on a vacation, the patient again used Psorcutan® Salbe for a slight recurrence of the psoriatic plaques on the lower legs. Within 2 weeks, she had developed a severe itchy exudative dermatitis. She stopped the topical drug and, when visiting the office after 1 week, the periphery of the psoriatic lesions still showed redness and small papules. In the centre of the plaques there were large crusts and scaling.

Contact allergy to a constituent of calcipotriol ointment was suspected. The lesions cleared com-

Table 1. Results of patch testing with Psorcutan® Salbe and its active ingredient

	1st test			Retest after 6 months	
	D2	D3	D4	D2	D3
Psorcutan® Salbe	+	+++	NT	++	+++
calcipotriol (in isopropyl alcohol)					
0 mcg/ml	0	0	0	0	0
0.08	0	±	0	0	±
0.40	0	0	0	±	+
2.0	+	++	++	±	++
10.0	++	+++	+++	±	+++
50.0	+++	+++	+++	+	+++

pletely under topical corticosteroid application followed by a bland ointment. Patch testing was performed 2 weeks later with Psorcutan® Salbe, the standard series, and supplementary allergens (vehicles series, preservatives). All materials were obtained from Hermal (Reinbek). Small Finn Chambers on Scanpor tape were used; application time was 2 days (D), readings were taken at D2, D3 and D4 according to well-known international guidelines (1).

4 months after the 1st patch testing, the patient

was tested with a concentration series of calcipotriol as provided by the manufacturer: 0.08 µg/ml, 0.4 µg/ml, 2.0 µg/ml, 10.0 µg/ml, 50 µg/ml. The vehicle was citrate-buffered isopropyl alcohol (pH 8.5). Simultaneously, a ROAT was performed on the volar aspects of the forearms with Psorcutan® Salbe on one side and with the calcipotriol-free ointment base on the other side. A small amount was rubbed onto an area of 5×5 cm 2 × daily using a cotton swab.

ROAT on volunteers. In order to obtain a baseline of the irritancy of Psorcutan® Salbe, 15 healthy subjects applied the commercial product in the same way as the patient on both forearms for 14 days.

Retesting of patient. 6 months after the 1st test with the calcipotriol concentration series, the patch test was repeated on the patient in the same way on normal back skin.

Results

The 1st patch testing showed a crescendo-type reaction to Psorcutan® Salbe amounting to a strongly infiltrated vesicular reaction at the D3 reading (Table 1). In the standard series (chloro) – methyl-

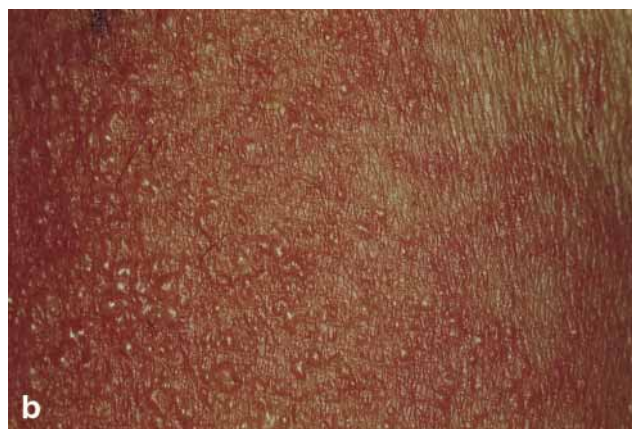
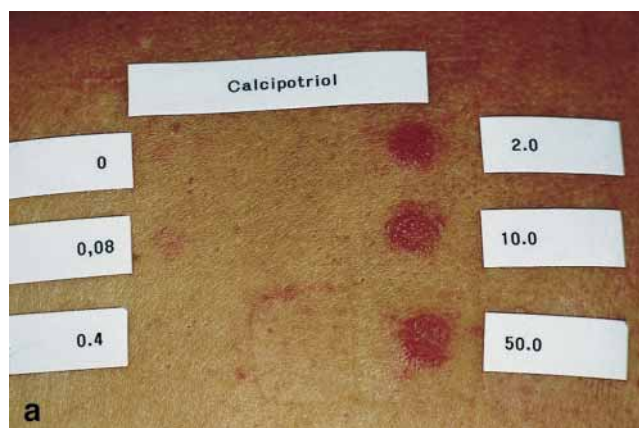


Fig. 1. Results of patch testing with a dilution series of calcipotriol (D 3, a)). Results of ROAT: papulovesicular dermatitis after 7 applications of Psorcutan® Salbe (b), no reaction to placebo ointment (c).

Table 2. Results of repeated open application test (ROAT) on forearms of patient and 15 volunteers

1. ROAT on patient

Psorcutan® Salbe	Placebo ointment
erythema, edema, papules, numerous vesicles; pruritus (after 4 days, 7 applications)	no reaction

2. ROAT on volunteers

Subjects	Psorcutan® Salbe (left)	Placebo ointment (right)
1	follicular erythema (day 5 and day 6) negative upon continuance until day 14	follicular erythema (day 6 only)
2	spotty erythema, beginning on day 11, no progression until day 14	same reaction as on left side
3–15	negative	negative

isothiazolinone (MCI/MI), developed a + reaction. All other tested materials, particularly propylene glycol (20% in water), a constituent of Psorcutan® Salbe, were negative.

The reaction to Psorcutan® Salbe was still visible after 2 weeks during a follow-up visit. In the 2nd patch testing, calcipotriol caused strongly positive reactions to concentrations of 2 µg/ml and higher (Table 1 and Fig. 1). All lesions were palpably infiltrated, showed papules and vesicles upon magnification and were itchy. Reactions to the next lower concentrations in the series were completely negative (0.4 µg/ml) and doubtful (erythema only) at D3 (0.08 µg/ml). Retesting after 6 months revealed again strong reactions to 2 µg/ml and higher concentrations of calcipotriol. Furthermore, there was now a definite + reaction at D3 to 0.4 µg/ml and a weak erythematous reaction to 0.08 µg/ml (Table 1).

Histology

A 4-mm punch biopsy from the ++ reaction to 2 µg/ml calcipotriol was taken after the D4 reading. Histological examination revealed spongiosis of the epidermis and marked perivascular infiltrates with lymphocytes, macrophages and eosinophils.

Repeated open application test (ROAT)

On the patient, Psorcutan® Salbe produced an itchy papulovesicular dermatitis with severe edema and redness after 7 applications, on the 4th day. The calcipotriol-free vehicle base remained completely negative (Fig. 1 and Table 2).

On 13 volunteers, the ROAT with the commercial product was completely negative on both forearms, even after an application period of 14 days. In 1 subject with a previous history of atopic hand dermatitis, a slight reaction with follicular erythema developed on D 5 (left) and D 6 (right). The reactions cleared despite further applications until D 14. In another subject with a history of hay fever, a similar weak reaction occurred by the end of the 2nd week (Table 2).

Discussion

This is a clear-cut case of contact allergy to calcipotriol. The patient developed marked irritation during the first weeks of application, but adapted to the agent at a lower frequency of usage in combination with a corticosteroid. Then, after a longer interval, reapplication of the calcipotriol ointment caused the typical picture of allergic contact dermatitis. The intensity of the reaction, with severe itching and burning, and the previously never-occurring exudation due to vesiculation prompted the patient to discontinue the ointment immediately. Patch testing with the used product as is supported the suspicion of contact allergy. Definite confirmation was obtained by clearly positive reactions in a dose – dependent and crescendo pattern to calcipotriol in isopropyl alcohol. The still doubtful critic may be convinced by the strongly positive ROAT within 4 days and the result of retesting after 6 months.

The patient was tested in the non-acute phase of her disease, was not atopic and had no history of “sensitive skin”. Therefore, irritant reactions can be ruled out.

At the concentration used in the marketed formulation for the treatment of psoriasis (50 µg/ml), calcipotriol seems to be a moderate irritant, particularly if applied under occlusion for a period of 1 to 2 days. The morphology of the reaction may be similar to weak or moderate allergic reactions. The intensity may even increase with late readings. This “delayed type of irritancy” has been observed with some irritants like sodium lauryl sulfate (7) or dithranol and, in particular, with hexanediol diacrylate (8). This last substance mimicked the clinical picture of contact allergy in workers using UV-cured paint containing this diacrylate in a door factory, and it required the considerable effort of such an experienced allergologist as Klaus Malten to identify the causative agent as an atypical irritant and not as a contact allergen. This paper is still very valuable today because of the clear description of both types of dermatitis, its overlap and difficulties in separation. Calcipotriol falls into this category. In patients with psoriasis, it fre-

Table 3. Clinical reports of contact allergy to calcipotriol. (ACD, allergic contact dermatitis); vehicle for patch testing was buffered isopropanol unless indicated otherwise

Author/ no. cases	Clinical picture	Reaction to used product	Calcipotriol – serial dilution patch testing $\mu\text{g/ml}$ (D3 or D4 reading)					ROAT pos. after days	Comment
			0.08	0.4	2.0	10.0	50.0		
this study 64 y. woman	ACD	Psorcutan® Salbe +++	0	±	++	+++	+++	+++ (D4)	
Yip & Goodfield (2) 68 y. woman	acute dermatitis	MC 903 ointment++ vehicle neg.	NT	NT	NT	NT	NT	NT	contact allergy not proven
Bruynzeel et al. (3) 50 y. woman	dermatitis	calcipotriol ointment+ placebo ointment. neg.	NT	NT	NT	+	+	NT	calcipotriol tested in ethanol as vehicle. Weak reactions to further Vitamin D ₃ analogues. (25-OH D 3, 1- α -OH D 3)
					retest after several months ++	++	++		
De Groot (4) 36 y. woman	red itchy dermatitis	calcipotriol ointment ++	0	0	+	+	NT	strongly pos. with calcip. ointm. (D3); calcip. 10 $\mu\text{g/ml}$ (isopropanol) pos. (D7) negative with lower conc. (0.4 and 2.0 $\mu\text{g/ml}$) after 3 months negative	3/26 controls tested with calc. 10 $\mu\text{g/ml}$ in isoprop. had a ?+ reaction at D2, negative at D3
Steinkjer (5) 64 y. man	exudative dermatitis	Daivonex® ointment. ++	0	?+	+	++	++	?+	no details on duration of ROAT
			retest after 3 months 0	0	?+	+	+		
Schmid (6) 54 y. woman	dermatitis, pruritus	Daivonex® ointment. ++ Retest after 3 months ++	?+	+	+	++	++	++ (D5–14) severe eczematous reaction; placebo ointm. neg.	histology of Daivonex® test reaction compatible with ACD; patch testing with serial dilution was done 8 months after 1st patch test with Daivonex®
Zollner et al. (13) 54 y. woman	ACD	Daivonex® ointment ++	0	+	+	++	++	+++ (D3) reproduced 6 months later	histology of patch test compatible with ACD; lymphocyte transformation test positive at 10 ⁻² M (5 controls negative). Tacalcitol patch test negative
Garcia-Bravo and Camacho (14) 54 y. woman	acute dermatitis	calcipotriol cream ++ retest after 6 months ++	NT	0	NT	NT	NT	+++ (D2?)	higher concen- trations of calc. in isopropanol were apparently not tested; patch testing with calcip. Cream as is in non-exposed controls: 6/26 irritant reactions at D2, negative at D4
				retest after 6 months 0					
Garcia-Bravo and Camacho (14) 62 y. man	generalized eczema	calcipotriol cream ++ retest after 6 months +++	NT	+	NT	NT	NT	ROAT negative	
				retest after 6 months +					

quently causes cumulative irritancy after 1 or 2 weeks of use. Sensitive skin regions and certain individuals seem to be predisposed.

The dermatitis may be papular or even vesicular and then simulate an allergic contact dermatitis. However, in certain cases it may also induce contact allergy. Table 3 lists, in addition to our own patient, at least 3 further cases that are convincing. Recently Zollner et al. (13) have also reported a clear case: patch test sensitivity was high (positive to 0.4 $\mu\text{g/ml}$), ROAT was strongly positive within 3 days with papulovesicles, reproducible after 6 months and (as the final proof of contact allergy) a lymphocyte transformation test with calcipotriol was positive.

The first report of Yip & Goodfield (2) remains doubtful because neither a ROAT nor serial dilution testing with calcipotriol was performed. The case report of Molin (9) is not listed in Table 2 because the author himself interprets the dermatitis in a 73-year-old man as unusual irritancy. After repeated use of calcipotriol ointment for 4 treatment periods over 2 years without any problems, the patient developed a severe itchy dermatitis within few days of reapplication in a double-blind trial in combination with UVB. In the open test the patient reacted with a vesicular dermatitis after only 6 applications and avoidance of UVB. 3 months later, patch testing with a dilution series of calcipotriol and an open test with the same ointment were both negative. Molin explains this event as an endogenous variation in the threshold of irritation, which may render selected patients more vulnerable to irritant events with limited periods of time.

The problem of irritancy when patch testing with calcipotriol has been discussed by several authors (3–6) and was the subject of recent extensive studies (10, 11). Fullerton et al. (10) examined 168 individuals (psoriatic patients treated with calcipotriol with dermatitis due to calcipotriol, psoriatic patients treated with calcipotriol with no dermatitis, psoriatic patients never treated with calcipotriol, patients with eczema and healthy volunteers) by patch testing with dilutions of calcipotriol ointment (50, 10, 2, 0.4 $\mu\text{g/ml}$) and an ointment vehicle. Test evaluation was based on clinical scoring and various non-invasive bioengineering methods. Doubtful and weak (+) reactions were common and irrespective of patient group and history. Moderate (++) reactions were uncommon and according to the conclusion of the authors “with no increased frequency among psoriatic patients with adverse dermatitis during calcipotriol treatment”. However, there was a non-significant trend that patients with a history of dermatitis due to calcipotriol had more frequently developed ++

reactions than patients without dermatitis. This is well visible in Fig. 2 of their publication, where a total of approximately 12% of 32 patients with calcipotriol dermatitis showed a ++ reaction starting at a concentration of 2 $\mu\text{g/ml}$. In contrast, ++ reactions were observed only in one further group (psoriatic patients treated with calcipotriol but no dermatitis), but at a much lower frequency of 2% and only at the highest concentration. Well in line was the finding that psoriatic patients with calcipotriol dermatitis showed a statistically significant increase of blood flow of their patch test reactions using laser Doppler flowmetry. The ROAT with Daivonex[®] ointment applied 2 $\times$ daily for 7 days was performed in all patients but, according to Fullerton et al. (10), none of the persons having a strong reaction in the patch test showed any definite dermatitis after the open use test. Faint erythema and papulofollicular reactions were observed only in 4 patients belonging to 3 different groups.

In the 1st and 2nd study of Fullerton et al., calcipotriol was found to be an irritant of the non-corrosive type. In the 2nd study (11), only healthy volunteers never exposed to calcipotriol were patch tested with various concentrations of calcipotriol in an isopropanol/citrate buffer solution, pH 8.5. The ointment vehicle was found to be slightly irritating in the 1st study due to propylene glycol, resulting in an increase in transepidermal water loss. In the 2nd study, the authors conclude that cases of suspected allergy should be patch tested with 2 $\mu\text{g/ml}$ in calcipotriol citrate buffered solution under occlusion for 2 days using small Finn Chambers. Scores of $\frac{1}{2}$ ($\pm$, erythema only) or + reaction may still be irritant. The test should be repeated after 3 months to ensure its consistency over time. A ROAT “may be indicated”.

Based on our own experience and the findings reported in the literature, we conclude the following. Contact allergy to calcipotriol should be suspected, if a severe dermatitis develops, particularly with vesiculation and itching. This may occur during continuous usage for the first time but is more likely to happen upon reapplication.

Patch testing with the ointment as is is non-conclusive, because the concentration of calcipotriol at 50 $\mu\text{g/ml}$ will produce irritant reactions in nearly everyone. Patch testing with a concentration series down to 0.08 $\mu\text{g/ml}$ calcipotriol in buffered isopropyl alcohol is necessary in order to determine the minimal eliciting concentration of the patient. If a strong (++ or ++++) reaction is observed at a concentration of 2 $\mu\text{g/ml}$ and this is reproduced after several weeks, contact allergy to this material is very likely. Further proof can be obtained by a positive ROAT. De Groot (4) recommends the use

of 2–10 µg/ml in isopropanol. We think that the commercial ointment can also be used; in case of contact allergy, a severe vesicular dermatitis will develop within 3 to 5 days, as shown by our case and those of de Groot (4), Schmid (6) and Zollner et al. (13). As the results of our control group demonstrate, the majority have not reacted at all to Psorcutan® ointment even when applied for 14 days. Only 2 atopic subjects developed a faint erythema, not comparable to the severe vesicular dermatitis of our patient, as shown in Fig. 1. Therefore, the ROAT with the commercial ointment for 7 days (maximum 14 days) is valuable to confirm the suspicion of an allergic sensitization based on the patch test results. Final proof can be obtained by a positive lymphocyte transformation test, if this procedure is accessible.

At this moment, contact allergy to calcipotriol seems to be rare. However, only a large prospective study of psoriatic patients with dermatitis, and without dermatitis, following the prolonged use of calcipotriol, will provide accurate figures on the sensitization rate. With dithranol, it took several decades until it was proven that adverse reactions were not all of the irritant type but that contact sensitivity also existed (12). There is already no doubt that calcipotriol may cause allergic contact dermatitis.

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Addendum

In the meantime, the patient was also patch tested with tacalcitol (4 µg/g in pet.) which was completely negative after 2 and 3 days, confirming the result of Zollner et al. (13) that there is no cross-reactivity between calcipotriol and tacalcitol.

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