

ORIGINAL ARTICLE

Allergic contact dermatitis caused by dexpanthenol—Probably a frequent allergen

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Background: Panthenol (synonym: dexpanthenol), the alcohol analogue of panthothenic acid, is frequently included in moisturizers, wound-healing agents, and other cosmetics, and has been shown to be responsible for allergic contact dermatitis (ACD).

Objectives: To evaluate the frequency of ACD caused by dexpanthenol, and to characterize reactive patients.

Methods: We retrospectively reviewed the files of patients patch tested between 2009 and 2017 in the Department of Dermatology of the Coimbra's University Hospital and describe patients who reacted to dexpanthenol 5% pet., tested initially in a cosmetic/vehicle series and in the last 3 years in consecutive patients.

Results: Among 2171 patients, 26 (1.2%) had positive patch test reactions to dexpanthenol, mostly patients tested for chronic eczema (88.5%, $n = 23$), either widespread (5), or localized to the hands (5), face (4), or legs (7). Relevance could be traced in 20 patients (76.9%), related to the use of Bepanthen cream (15), moisturizers (3), topical medications (1), and a shampoo (1). Twenty-five of 26 patients (96.2%) reacted to several other allergens, mostly ingredients of cosmetic or pharmaceutical products.

Conclusions: Although ACD caused by dexpanthenol is considered to be rare, it may be frequently overlooked. As we found a relatively high frequency of relevant cases, in agreement with a previous study, the inclusion of dexpanthenol in patch test series, at least in cosmetic and topical drug series, is encouraged.

KEYWORDS

allergic contact dermatitis, CAS no. 81-13-0, cosmetics, dexpanthenol, patch test, topical medication

1 | INTRODUCTION

Dexpanthenol (INCI name panthenol; CAS no. 81-13-0) is the alcohol analogue of panthothenic acid, known as vitamin B5. It is essential for the cellular biosynthesis of coenzyme A, which has a role in conveying acetyl groups to the Krebs cycle in order to generate energy.^{1,2} Only the D-stereoisomer, D-panthenol, is biologically active.¹ Dexpanthenol is widely used in the pharmaceutical and cosmetic industries for its moisturizing and soothing properties.² It improves epidermal barrier disruption, reducing transepidermal water loss and improving

hydration of the stratum corneum,³ accelerates skin re-epithelialization, and activates fibroblast proliferation; it is therefore used as a wound-healing promoter for ulcers, bed sores, excoriations, burns, and sunburn.^{3,4} Dexpanthenol is also included in topical drugs for rhinitis and conjunctivitis.²

Allergic contact dermatitis (ACD) caused by dexpanthenol is considered to be relatively uncommon,⁵ but has been reported following the use of medications, moisturizers, and sunscreens.¹ The allergic moiety of dexpanthenol involved in ACD remains uncertain. Inside the cell, dexpanthenol is rapidly converted to pantothenic acid and

one of its components, β -alanine, which could also possibly play a role in the induction of ACD.⁶ Lymphocyte transformation tests with dexpanthenol-modified microsomes performed by Hahn et al⁴ suggested a specific T cell-dependent reaction enhanced by microsomal-dependent antigen metabolism.

In the present analysis, we evaluated the frequency of sensitization to dexpanthenol and the characteristics of sensitized patients diagnosed by aimed testing between 2009 and 2014 and by patch testing in consecutive patients between 2015 and 2017.

2 | METHODS

Dexpanthenol 5% pet. (allergEAZE, Calgary, Canada) has been patch tested in the cosmetic/vehicle series since 2009; from 2015, it has been included in the baseline series of the Department of Dermatology of the University Hospital Coimbra. Between 2009 and 2014, among 1882 patch tested patients (500 males and 1362 females), 1117 (300 males and 817 females) were subjected to aimed testing with dexpanthenol in the complementary series because of the suspicion of ACD caused by cosmetics or topical drugs, or occupational dermatitis resulting from exposure to cleansing lotions and emollients. Between January 2015 and December 2017, all 1054 consecutive patients (311 males and 743 females) were tested with dexpanthenol.

The allergens were placed in 8-mm Finn Chambers on Scanpor tape (allergEAZE, Calgary, Canada), and immediately applied on the patient's upper back. Allergens were left in place for 2 days, and readings were performed on day (D) 2 or D3, and between D4 and D7, according to ICDRG and ESCD recommendations.⁵ Only patients with positive reactions, including weak (+), strong (++) and extreme (+++) reactions, were evaluated further. Demographic and clinical profiles of patients with positive reactions were collected and compared with those of the whole population tested by use of the MOAHLFA index (Male, Occupational, Atopy, Hand, Leg, Face, Age $\geq$ 40 years). Relevance was evaluated according to exposure history, relationship with the patient's dermatitis, and patch testing with patients' own products. Comparison of categorical data was performed with χ^2 analysis and Fisher's exact test with a 2-tailed *P*-value. A *P*-value of $< .05$ was considered to be significant.

3 | RESULTS

During the study period, among a total of 2171 patients, 26 (1.2%) were found sensitized to dexpanthenol: 13 of 1054 consecutively

tested patients (1.23%), and 13 of 1117 tested with the complementary series (1.16%) (Table 1). Patients with positive reactions included 18 females and 8 males, and were aged 15 to 75 years (median 51.5 years). A background of personal atopy was identified in 6 patients (23%), and atopy in the family in 3 patients (11.5%). The most common presentation was chronic eczema (88.5%, $n = 23$), with a median evolution of 24 months (range 1 month to 20 years). Lesions were widespread ($n = 5$) or localized mainly to the hands ($n = 5$), face ($n = 5$), and/or legs ($n = 7$), in these latter cases associated with chronic venous insufficiency and/or chronic leg ulcer.

Reactions were considered to be relevant in 20 of 26 patients (76.9%). They were all exposed as consumers, 15 of them to Bepanthen cream or ointment (Bayer, Carnaxide, Portugal), which contains 5% dexpanthenol. In 5 patients, we identified exposure to dexpanthenol in moisturizers ($n = 3$), topical medications ($n = 1$), and a shampoo ($n = 1$). In 6 patients (23.1%), we could not identify current exposure to dexpanthenol.

One patient was exclusively sensitized to dexpanthenol: a 32-year-old woman with a 2-year history of eczema localized to a skin graft where she applied ATL cream (Edol, Linda-a-Velha, Portugal), which contains 2% dexpanthenol. Twenty-five patients reacted to several other allergens or topical products, 17 of them (65.4%) to ingredients of cosmetic or pharmaceutical products, for example, lanolin alcohol and/or Amerchol L101 ($n = 7$), cetostearyl alcohol ($n = 4$), methylisothiazolinone ($n = 4$), nonoxynol-9 ($n = 4$), fragrance mix I ($n = 5$), and fragrance mix II ($n = 1$). Patient details and patch tests results are summarized in Tables 2 and 3.

4 | DISCUSSION

ACD caused by dexpanthenol seems to be rare in relation to its long-standing and widespread use in different topical preparations.¹ Bepanthen cream, which was most frequently implicated in our study, was launched in Switzerland in 1944.⁷ In 1995, Schmid-Grendelmeier et al reported 7 cases of allergy to dexpanthenol,⁸ and reviewed the literature summarizing 40 published cases up to 1995. Since then, a few other cases have been reported,^{2,5,6,8,9} and, in 2017, Clerens and Goossens published a review of 23 patients with ACD caused by dexpanthenol among 3301 patients patch tested with dexpanthenol 5% pet. between 1990 and 2016, amounting to 0.7%,¹ a frequency that is very similar to that in our study (0.89%). Two cases of ACD caused by dexpanthenol were reported in children,^{1,3} but all age groups seem to be affected, as in our study, with the age of cases ranging from 15 to 75 years. There is also

TABLE 1 Number of patients tested with dexpanthenol 5% pet. and number and percentage of positive results

		Total	Dexpanthenol-positive, <i>n</i> (%)	Current relevance, <i>n</i> (%)
Aimed testing (2009-2014)	Total	1117	13 (1.16)	9 (69.2)
	Male	300	2 (0.7)	0
	Female	817	11 (1.3)	9 (100)
Consecutive patients (2015-2017)	Total	1054	13 (1.23)	11 (84.6)
	Male	311	6 (1.9)	4 (36.3)
	Female	743	7 (0.9)	7 (63.7)

TABLE 2 Characteristics of patients with positive patch test reactions to dexpanthenol diagnosed by aimed testing (2009-2014)

	Sex, age (years)	Eczema localization	Positive patch test results		
			Dexpanthenol 5%	Commercial preparations	Other positive patch test results
1	F, 52	Eyelid	D2 +/D4 ++	Bepanthen cream ++ Betadine ointment ++ Halibut cream ++	-
2	F, 26	Hand	D2 ++/D4 ++	Eucerin hand cream ++	Cobalt 1% +++
3	F, 15	Disseminated	D2 +/D4 ?+	-	Nickel 5% ++
4	F, 30	Face	D2 +/D4 ++	Bepanthen cream +++ Fenistil gel ++ Zovirax cream ++	Cetearyl alcohol 20% ++
5	F, 74	Leg (chronic ulcer)	D2 ++/D4 ++	Biafine cream ++ Nadiclox ointment ++ Silver sulfadiazine cream ++	Fragrance mix I 8% ++ Amerchol L101 50% ++ Diazolidinyl urea ++ Imidazolidinyl urea 2% ++ Fusidic acid 2% ++ Hydrocortisone 1% ++
6	F, 21	Axilla	D2 ++/D4 +	Deodorant La Roche Posay ++	Fragrance mix I 8% ++
7	M, 73	Leg ulcer	D2 ++/D4 ++	Mitosyl ointment ++	Lanolin alcohol 30% ++ Amerchol L101 50% ++ Benzocaine 5% ++ Nonoxynol-9 2% ++ Thiuram mix 1% ++
8	F, 75	Leg ulcer	D3 ++/D5 ++	Bepanthen cream ++ Ulcerase ointment ++	Amerchol L101 50% ++ Cetostearyl alcohol 20% ++ Polyvinylpyrrolidone-iodine 2% ++ Nonoxynol-9 2% ++
9	M, 75	Leg ulcer	D4 +/D6 ++	-	Nickel 5% ++ Fusidic acid 2% ++ Benzotriazole 1% ++
10	F, 60	Abdomen	D2 ++/D3 +	Bepanthen cream ++ Biafine cream ++	MDGBN 0.3% +++ Propylene glycol 20% ++ Nonoxynol-9 2% ++
11	F, 20	Face, hand	D3 +/D7 ?+	-	Nickel 5% + Cobalt 1% +
12	F, 34	Arm, forearm	D2 ++/D5 +	Bepanthen cream + Bepanthen ointment +	Gentamicin 20% ++ Chlorhexidine 0.5% ++
13	F, 60	Disseminated	D4 ++/D6 ++	Bepanthen cream +++ Fenergan cream +	Fragrance mix I 8% + Evernia prunastri +

Abbreviations: D, day; F, female; M, male; MDGBN, methylidibromoglutanitrile. Preparations that contain dexpanthenol are in bold.

one report of a severe systemic reaction induced by dexpanthenol in multivitamin tablets after previous use of a sunscreen cream containing dexpanthenol.¹⁰

Although ACD caused by dexpanthenol is considered to be rare, with the frequency in previously reported series ranging from 0.2% to 0.7%,¹¹ we found 1.16% positive reactions when it was tested in the cosmetic/vehicle series, and a slightly higher proportion of 1.23% in the last 3 years when it was tested in consecutive patients; this was a non-significant difference between the 2 types of testing. This suggested to us that almost all patients sensitized to this hapten are detected with aimed patch testing, that is, if the allergen is included in a cosmetic series and a series of vehicles for topical drugs.

In our series, contact allergy to dexpanthenol is more common in women (69.2%), but this is not significantly different from the percentage of women patch tested in our department (63.4%). With consecutive testing, there was a 3-fold increase in the diagnosis of this sensitization in males, which may suggest that, in males, clinicians tend to overlook the possibility of ACD caused by this contact allergen. Personal atopy and atopic dermatitis (23%) are not more frequent

than in the general population (31.3%), even though dexpanthenol is widely used to improve the epidermal barrier. On the other hand, the diagnosis of chronic leg ulcer is overrepresented in this patient series (26.9%) as compared with the whole population (8.3%) ($P < .01$). This may suggest its widespread use in this population or, as previously reported, indicate that patients with chronic venous insufficiency and dermatitis are more prone to become sensitized to the active chemicals and vehicles of topical drugs (Table 4).¹² In our series, 25 patients (96.1%) were polysensitized, and 17 (65.1%) reacted to several ingredients of cosmetic or pharmaceutical products. As in the study of Clerens and Goossens,¹ facial and hand dermatitis were also frequent, although less common than in the whole population tested.

Current relevance of contact allergy to dexpanthenol could be definitively traced in 76.9% of our cases, which is lower than the frequency in the previous review, in which all cases were relevant.¹ With a more careful investigation, we might have identified additional previous exposures to topical drugs or cosmetics containing dexpanthenol, particularly in the 7 patients who suffered from chronic leg ulcer.

TABLE 3 Characteristics of patients with positive patch test reactions to dexpanthenol tested in consecutive patients (2015-2017)

	Sex, age (years)	Eczema location	Positive patch test results		
			Dexpanthenol 5%	Commercial preparation	Other positive patch test results
1	F, 56	Hand	D4 ++/D6 ++	Bepanthen cream ++ Bepanthen ointment D4 ++	Fragrance mix I 8% +++ Fragrance mix II 14% +++ HICC 5% ++ Citral 2% ++ Quaternium-15 1% ++ MDGBN 0.3% ++
2	M, 48	Leg ulcer	D3 +/D4 ++	Fucidine H cream +++	Paraben mix 16% ++ Lanolin alcohol 30% +++ Amerchol L101 50% ++ Fragrance mix I 8% ++ Sorbitan sesquioleate 20% +++ Propolis 10% ++ Stearyl alcohol 20% ++ Triethanolamine 2.5% ++ Benzalkonium chloride 0.1% ++ Polyvinylpyrrolidone-iodine 2% ++ Nonoxynol-9 2% +++
3	F, 43	Disseminated	D4 ++/D6 ++	Bepanthen cream ++	Formaldehyde 1% ++
4	F, 30	Face (lip), abdomen	D4 +/D6 ++	-	Nickel 5% +
5	F, 32	Skin graft	D4 +/D6 +	-	-
6	M, 51	Arm V of neck	D4 +/D6 ++	-	PPD 1% +++ N-Isopropyl-N'-phenyl-PPD 0.1% +++ Carba mix 3% ++
7	M, 73	Leg ulcer	D4 ++/D6 ++	-	Lanolin alcohol 30% +++ Amerchol L101 50% +++
8	F, 71	Face	D4 ++/D5 ++	Bepanthen cream ++ Bepanthen ointment ++	Neomycin 20% + Benzoic acid +
9	F, 47	Face Hand, arm	D2 ++/D4 ++	Bepanthen cream D2+++ Bepanthen ointment ++ Biafine cream ++	Lanolin alcohol 30% ++ Amerchol L101 50% ++ Colophonium 20% ++ Cobalt chloride 1% +++ Potassium dichromate 0.5% ++ Phenol-formaldehyde resin 1% ++
10	M, 67	Knee	D3 +/D5 +	-	Carba mix 3% ++ MI 0.2% ++ HEMA 1% 5+
11	M, 68	Disseminated	D3 ++/D5 ++	-	Potassium dichromate 0.5% ++ Lanolin alcohol 30% ++ Amerchol L101 50% ++ MI/MCI 100 ppm ++ Cetearyl alcohol 20% ++ Bacitracin 20% +++ Polymyxin B 3% ++ Clotrimazole 5% ++
12	M, 32	Hand	D3 +/D5 +	-	MI/MCI 100 ppm D3 +/D5 + MI 0.2% D3 +/D5 +
13	F, 75	Leg ulcer	D3 +/D5 +	Bepanthen cream +++	Paraben mix 12% ++ MI 0.2% ++

Abbreviations: D, day; F, female; HEMA, hydroxyethyl methacrylate; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; M, male; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; PPD, p-phenylenediamine. Preparations known to contain dexpanthenol are in bold.

TABLE 4 Comparison of the MOAHLFA index between the whole population tested between 2009 and 2017 and the group of dexpanthenol-positive patients

	Whole population (%)	Dexpanthenol-positive n (%)	P-value
Male	36.2	8 (30.8)	.68
Occupational	25.1	0	-
Atopy	31.1	6 (23.1)	.36
Hand	43.2	5 (19.2)	.015
Leg	8.0	7 (26.9)	.004
Face	34.2	5 (19.2)	.11
Age > 40 years	73.8	17 (65.4)	.27

Note: associations that are significant are in bold.

5 | CONCLUSIONS

Although contact allergy to dexpanthenol seems to be rare, it has been shown to be a frequent and relevant contact allergen, both in topical drugs and in cosmetics. Therefore, this hapten should be included in cosmetic and vehicle series for patch testing. Although most reactions were found when testing was performed with the complementary series, the reactivity of >1% found in consecutive patients associated with a high relevance could also favour inclusion in a baseline series.

Conflict of interest

The authors declare no potential conflict of interests.

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