

Erythema multiforme-like reaction resulting from vitamin K₁ oxide (phytomenadione epoxide)

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Erythema multiforme-like reaction, also called urticarial papular and plaque eruption, is an uncommon non-eczematous clinical variant of allergic contact dermatitis; its pathogenesis is unknown. Many allergens have been reported as causes of erythema multiforme-like reactions, such as different woods and plants, topical medicines, metals, and chemicals such as *p*-phenylenediamine (1). Erythema multiforme-like reactions have not been associated with topical vitamin K₁ or vitamin K₁ oxide exposure thus far.

Case Reports

Case 1

A 6-year-old healthy boy acutely developed an itchy reaction involving the right side of his face, neck, shoulder, and ipsilateral upper limb, consisting of coalescent targetoid erythematous papules. On the affected skin areas, his mother had started to apply Arnika gel® (Martiderm, Cervelló, Spain), containing vitamin K₁ oxide, 2 weeks



Fig. 1. Coalescing targetoid erythematous papules involving the areas where a topical product containing vitamin K₁ oxide had been applied on the patient's face, neck, and arm.

before (Fig. 1) with the aim of lessening symptoms resulting from a car accident 1 month before. Avoidance of the gel and application of a topical corticosteroid led to the clearance of the lesions in < 1 week.

The patient was patch tested with the gel 'as is', the Spanish Contact Dermatitis Research Group (GEIDAC) baseline series supplied by AllergEaze (Calgary, Canada), and the individual ingredients at concentrations as used in the product provided by the manufacturer. The

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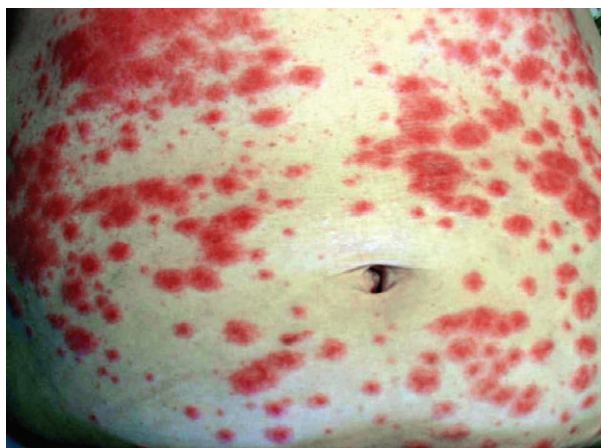


Fig. 2. Erythematous 'targetoid' papules involving the areas where, 2 weeks before, a mesotherapy procedure had been performed on the second patient's abdomen. A topical product containing vitamin K₁ oxide had been applied in the following days.

allergens were prepared on Curatest[®] chambers (Lohmann & Rauscher, Neuwied, Germany), applied on his back, and fixed with Omnifix E[®] (Hartmann, Heidenheim, Germany). Both exposure times and the performance and scoring of readings were according to international guidelines (2). Positive results were obtained with the product 'as is', namely, ++ on day (D) 2 and D4, vitamin K₁ oxide (5% pet.) (+ on D2 and D4), and fragrance mix I. Further tests with the fragrance series supplied by Chemotechnique (Vellinge, Sweden) yielded positive results with isoeugenol (+++ on D2 and D4) and trimethylbenzenepropanol (synonym: majantol) (+ on D2 and D4). The manufacturer confirmed the absence of these fragrances in the product.

Case 2

A 35-year-old female patient presented with pruritic erythematous 'targetoid' papules involving those areas on her abdomen where, 2 weeks before, a mesotherapy procedure had been performed. The patient claimed that the rash had started at the periphery of the mesotherapy puncture spots, and then spread diffusely on her abdomen (Fig. 2). A skin biopsy showed acanthosis, spongiosis, and isolated necrotic keratinocytes.

The patient was patch tested with the GEIDAC baseline series provided by AllergEaze, cosmetic and fragrances series supplied by Chemotechnique, and the antiseptics and moisturizers that the patient had used during and after the mesotherapy procedure, tested 'as is'. The exposure time was 2 days, and readings were performed and results scored according to international guidelines (2).

Positive results (+++ on D7) were obtained only with a topical product containing vitamin K₁ oxide, namely, the same brand of Arnika gel[®] (Martiderm) that had been applied on the abdomen during the first days following the mesotherapy procedure. Additionally, patch and intra-dermal tests were performed with the injected mesotherapy extracts, with negative results. None of these extracts was known to contain vitamin K₁ or vitamin K₁ oxide. A biopsy of the positive patch test reaction was taken, and changes consistent with eczema, such as spongiosis and intraepidermal vesicles, were observed. Further patch tests with the individual ingredients of the Arnika gel[®] provided by the manufacturer were performed, and a positive result was obtained with vitamin K₁ oxide (5% pet.) (+++ on D7).

Discussion

Phytonadione (CAS no. 84-80-0) (INN phytomenadione), with the chemical name 2-methyl-3-(3,7,11,15-tetramethyl-2-hexadecenyl)-1,4-naphthalenedione, is one of the two natural isoforms of vitamin K. Vitamin K is involved in the biosynthesis of prothrombin and several coagulation factors (VII, IX, and X). Vitamin K deficiency predisposes to haemorrhagic conditions. In Spain, there are two parenteral formulations: Konakion[®] (used in vitamin K-related hypoprothrombinaemia secondary to liver, biliary tract or intestinal diseases, as well as a treatment for anticoagulant overdose); and Vitalipid[®] (used in parenteral nutrition in association with other liposoluble vitamins). Topical use of vitamin K has been recommended to treat purpura and hyperpigmentation secondary to trauma, or following surgical or laser procedures.

Parenteral vitamin K has been reported to cause delayed hypersensitivity skin reactions, which may be eczematous or morphea-like, surrounding the puncture sites, or have a diffuse patchy distribution (3–6). Immediate reactions (anaphylaxis) have also been described in relation to either the vitamin itself or the vehicle, namely polyethoxylated castor oil (7, 8). In addition, vitamin K₃ sodium metabisulfite has been related to allergic contact dermatitis in veterinarians or pharmacists (9, 10).

In the past, many cases of allergic contact dermatitis caused by topical vitamin K were reported in Italy, Spain, and France (11–15) (Table S1), which is why vitamin K was banned from use in cosmetic products in the EU in 2009 (16). The intention has been to use vitamin K₁ oxide (CAS no. 25486-55-9; synonym, 2,3-epoxyphytyl)menaquinone; INCI name, phytonadione epoxide) to replace vitamin K in cosmetics. Only two articles, including 4 cases of allergic contact dermatitis caused by vitamin K₁ oxide in cosmetics, have been

published thus far (17, 18), and none of these patients has shown erythema multiforme-like features (Table S2). It has been proposed that vitamin K₁ and vitamin K₁ oxide might cross-react. Hence, patch testing with vitamin K₁ can be used to diagnose vitamin K₁ oxide contact allergy if vitamin K₁ oxide is unavailable.

Cosmetic product labels of nine brands available in Spain were examined for the presence of vitamin K₁ oxide. Only six products belonging to three brands contained vitamin K₁ oxide: Arnika gel[®], Auriderm[®] (Isdin, Barcelona, Spain), K-Ox-Eyes[®] (Isdin), AngioSes[®] (Sesderma, Rafelbunyol, Spain), K-vit[®] (Sesderma), and Cernor XO[®] (Auriga International, Mons, Belgium).

To conclude, we would like to stress the following facts:

- Both vitamin K and vitamin K₁ oxide in cosmetics may sensitize consumers.
- Sensitization to vitamin K₁ oxide via cosmetics will jeopardize systemic treatment with parenteral vitamin K for significant internal diseases.
- Restrictions on the use of vitamin K₁ oxide in cosmetics are thus needed.

- Vitamin K₁ oxide should be included in the list of substances that are able to induce erythema multiforme-like reactions.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. English-language literature review. Contact dermatitis from vitamin K₁ in cosmetic products.

Table S2. Literature review. Contact dermatitis from vitamin K₁ oxide in cosmetic products.

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TABLES

ONLINE SUPPLEMENTAL TABLE 1. ENGLISH-LANGUAGE LITERATURE REVIEW. CONTACT DERMATITIS FROM VITAMIN K₁ IN COSMETIC PRODUCTS.

AUTHOR /(YEAR)	Case	COUNTRY	SEX	AGE	PRODUCT	INDICATION	LOCALIZATION	PATCH TESTS RESULTS
Veneziano/ (2005)	1	Italy	F	27	Auriderm K2 [®]	Periorbitary pigmentation	Periorbital	Auriderm [®] as is: positive (D2 and D3); vitamin K ₁ (2% pet.): +(D2), ++ (D3); <i>trans</i> -vitamin K ₁ (2% pet.) + (D2), ++ (D3)
Serra- Baldrich/ (2005)	2	Spain	F	45	Clarifying cream	Rosacea	Face	Vitamin K 1% pet. and 10% pet.: positive; ROAT cream as is: positive.
Ruíz- Hornillos/ (2006)	3	Spain	F	37	Eye contour cream (Ureadin Facial eye	Periorbital pigmentation	Periorbital and lips	Ureadin Facial eye contour [®] as is: +++; Konakion (1 mg/ml) sol. Aq.+++;

					contour [®])			Placebo negative
	4	Spain	F	36	Eye contour cream (Ureadin Facial eye contour [®])	Periorbital pigmentation	Periorbital	Ureadin Facial eye contour [®] as is: +++; Konakion (1 mg/ml) sol. Aq.+++; Placebo negative
López-Lerma/ (2006)	5	Spain	F	23	“Antiwrinkles cream”	Periorbital wrinkles	Eyelids	Cosmetic cream as is: ++ (D2 and D4); Vitamin K ₁ (2%) ++ (D2 and D4)
Ramírez-Santos/ (2008)	6	Spain	F		Eye contour cream (Ureadin Facial eye contour [®])	Psoriasis		Ureadin [®] as is: ++; vitamin K ₁ (1% pet) , Konakion
	7	Spain	F		Auriderm K5 [®]	-		Auriderm [®] as is: ++; vitamin K ₁ (1% pet); Konakion

**ONLINE SUPPLEMENTAL TABLE 2. LITERATURE REVIEW. CONTACT DERMATITIS FROM VITAMIN K₁ OXIDE IN
COSMETIC PRODUCTS.**

AUTHOR /(YEAR)	CASE	COUNTRY	SEX	AGE	PRODUCT	INDICATION	BODY SITE	CLINICAL FEATURES	DIAGNOSTIC TESTS RESULTS
García Gavín/ (2010)	1	Spain - Belgium	F	47	Auriderm XO [®]	After pulsed laser varicose veins therapy	Legs (anterior)	Perifollicular papules	Auriderm [®] (patch test): ++; Vitamin K ₁ oxide 1% pet. (patch test): ++
	2		F	63		Post- radiotherapy telangiectasia	Right breast	Dermatitis (NS)	
	3		F	51		Varicose veins surgery	Legs	Perifollicular papules	Auriderm [®] (patch test): +
Aerts/ (2012)	4	Belgium	-	-	Auriderm XO [®]	Surgery	Generalized	Dermatitis (NS)	Auriderm [®] (patch test): ++ (D4); Konakion [®] 10 mg/ml (patch test): ++ (D4); Konakion [®] 10 g/ml (intradermal): +++ (D4); Konakion [®] 10 mg/ml (prick test): negative;

									Konaktion [®] 1 mg/ml (patch test): + (D4)
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