Allergic Contact Dermatitis from the Vehicle Components of Topical Pharmaceutical Products

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KEYWORDS

• Allergic contact dermatitis • Iatrogenic • Topical pharmaceutical products
• Excipients • Preservatives • Fragrances

KEY POINTS

- The different categories in which the most important allergens can be classified are excipients, preservative agents, antioxidants, and fragrance components.
- The most frequently encountered allergens among the excipients are wool alcohols, propylene glycol, sorbitan oleate esters, and cetyl- en stearyl alcohol.
- The most frequently encountered allergens among the preservative agents are thimerosal, parabens, benzoic acid, and mercurials.
- The most frequently encountered allergens among the antioxidants are ethylene diamine (complexing agent) and (bi) sulfites.
- The most frequently encountered allergens among the fragrance components found in topical drugs are essential oils.

INTRODUCTION

The local application of pharmaceutical products may induce allergic and photo-allergic contact dermatitis (and, in some cases, skin reactions after systemic administration of the allergen or a chemically related compound), contact urticaria (immediate-type reactions), irritation, and systemic adverse effects caused by drug absorption. This article will only discuss allergic contact dermatitis.

ALLERGIC CONTACT DERMATITIS FROM TOPICAL PHARMACEUTICAL PRODUCTS

Topical pharmaceutical products are, in general, applied to diseased or inflamed skin, the barrier function of which is often incapacitated, leading to enhanced skin penetration of the applied chemicals. In such cases, even weak allergens are able to induce

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sensitization. Hence, contact allergy to topical pharmaceutical products is common, particularly in subjects suffering from stasis eczema and/or leg ulcers, perianal dermatitis, and otitis externa, but also in individuals with irritant and/or other pre-existing eczematous conditions.[1–4]

NATURE OF THE CONTACT ALLERGENS

The contact allergens in topical pharmaceutical products concern active principles and vehicle components. Not only products such as creams, ointments, and solutions, but also wound dressings may be involved.

This article will concentrate on the vehicle components. **Box 1** gives the number of cases with positive patch-test reactions to vehicle components of topical pharmaceutical products (ie, excipients, preservative agents, and fragrances). The allergens have been identified in a total population of 17,367 patients tested between 1990 and 2013, of whom 2513 (14.5%) presented with an allergic iatrogenic contact dermatitis.

The different categories in which the most important allergens can be classified are listed in **Box 1**.[1,2]

Excipients

Excipients include wool alcohols (eg, eucerin and lanolin), propylene glycol, sorbitan oleate esters, and cetyl- en stearyl alcohol. **Fig. 1** shows a positive reaction to isopropyl myristate. **Fig. 2** shows clinical symptoms and positive patch-test reaction to cetyl alcohol in a 15-month-old atopic baby, due to its presence in a pharmaceutical cream.

Preservative Agents

Preservative agents include thimerosal, parabens, benzoic acid, mercurial, and benzalkonium chloride. **Fig. 3**: shows contact dermatitis from a combination preparation containing a local antibiotic and corticosteroid caused by the preservative potassium sorbate (sorbic acid also positive).

Antioxidants

Antioxidants include ethylene diamine (complexing agent), previously the main allergen in a combined antimycotic/antibiotic/anti-inflammatory widely used cream, (bi) sulfites (test substance sodium metabisulfite),[5] and butylhydroxyanisole.

Perfume Components

Previously these were often present in historical wound-healing preparations, but they actually are still used in many preparations, including nonsteroidal anti-inflammatory products, which for example contain lavender, geranium-, or other essential oils. Indeed, in a previous study, the author could demonstrate that 10% of the topical pharmaceutical products in Belgium were found to contain fragrance components.[6] **Fig. 4** shows allergic contact dermatitis from fragrance components, including lavender oil in a nonsteroidal anti-inflammatory product.

Wound dressings

In general, wound dressings mainly contain higher molecular (polymeric) compounds that are less likely to induce sensitization, and thus seem to be safer than the previously used creams and ointments; however, some additives, particularly in hydrocolloids, such as modified colophony or antioxidants, may still be the allergenic culprits.[7,8]

Box 1
Allergic contact dermatitis from excipients (ie, vehicle components, preservatives, and fragrances in topical pharmaceutical products) (K.U. Leuven, 1990–2013)

Nr + Cases	Allergens
Vehicle components	
354	Wool alcohols
146	Propylene glycol
132	Sorbitan sesquioleate
77	Cetyl alcohol
66	Nonoxynol 9
21	Lauraminoxide
14	Benzyl alcohol
12	Polyethylene glycol
12	Olive oil
10	Stearyl alcohol
9	Sodium sulforicinate
8	Modified colophonium
7	Sesame oil
7	Isopropyl myristate
5	Glycerol monostearate
4	Triethanolamine
4	Polyethyleneglycol stearate
4	Hexylene glycol
3	Polysorbate 60
3	Polyethylene glycol glyceryl 20 oleaat
2	Sorbitan monolaurate
2	Polysorbate 80
2	Petrolatum
2	Eucerin
2	Almond oil (sweet)
2	Lactic acid
2	Laureth-9
2	Propyleneglycol monostearate
2	Beeswax
1	Polyethyleneglycol distearate
1	Hydroxyethylmethylacrylate
1	Butylene glycol
1	Glyceryl rosinate
1	Cetearyl glucoside
1	Myristyl alcohol
1	Castor oil
1	Diethanolamine
1	Ethyleneglycol monostearate
Preservative agents	
81	Thiomersal
65	Parabens
33	Benzoic acid
27	Phenylmercuriborate
26	Benzalkonium chloride
15	Chlorocresol
12	Sorbic acid
10	Imidazolidinylurea
10	Formaldehyde
9	Potassium sorbate
5	Phenylmercurinitrate
3	Fenoxyethanol
3	Diazolidinylurea
1	Quaternium 15
1	Propyl gallate
1	Phenylmercutiacetate

Antioxidants	
62	Ethylenediamine
38	Sodium metabisulfite
21	Butylhydroxyanisole
4	Disodium Edetate (EDTA)
2	Butylhydroxytoluene
Fragrances[a]	
88	Fragrance-mix I[b]
68	Balsam of Peru
31	Lavender oil
15	Perfume
10	Geranium oil
8	Orange flower oil
6	Eucalyptus oil
4	Terpineol
4	Fragrance-mix II[b]
3	Pine tree oil
2	Thyme oil
2	Niaouli oil
2	Rose oil
1	Jasmin oil
1	Clove oil
1	Nutmeg oil
1	Rosemary oil

14,367 subjects patch tested, 2514 with iatrogenic dermatitis.
[a] Some of these component are also used for other purposes than perfuming (eg, for their antiseptic properties).
[b] Markers for fragrance allergy tested in the baseline series.



Fig. 1. Positive reaction to isopropyl myristate (tested as is).

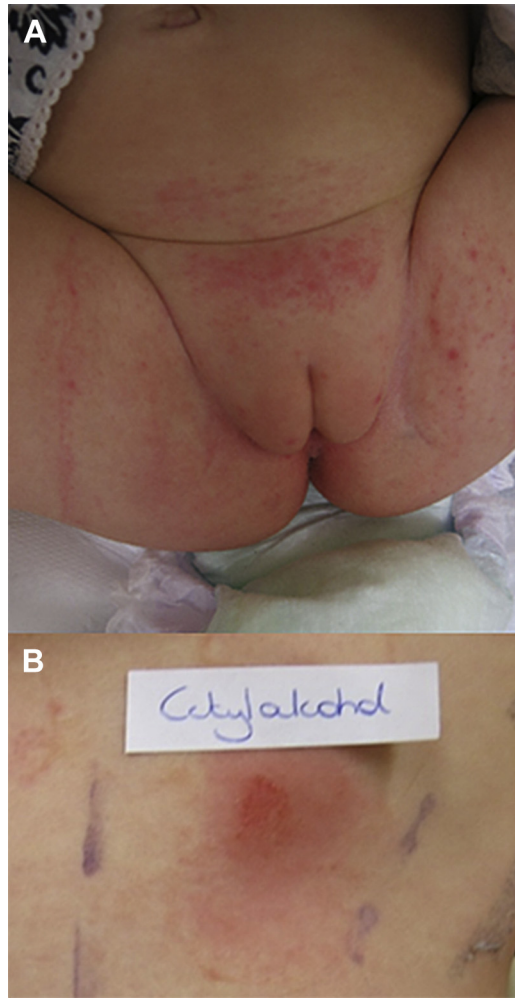


Fig. 2. (*A*, *B*) Clinical symptoms and positive patch-test reaction to cetyl alcohol in a 15-month-old atopic baby, due to its presence in a pharmaceutical cream.

DIAGNOSIS OF ALLERGIC CONTACT DERMATITIS

Patch (or epicutaneous) testing is the universally accepted method for the detection of causative agents. The test conditions for most of the contact allergens can be found in the literature.[9] Testing with the topical products used is also highly recommended; open and semiopen or semiocclusive tests,[10] use tests,[11] and repeated open application tests (ROATs)[12] are useful additional methods to identify the culprits.

Patch-Tests

Allergens, usually incorporated in petrolatum (sometimes also another vehicle), are applied in round or square chambers, which are mounted on adhesive tape, on the

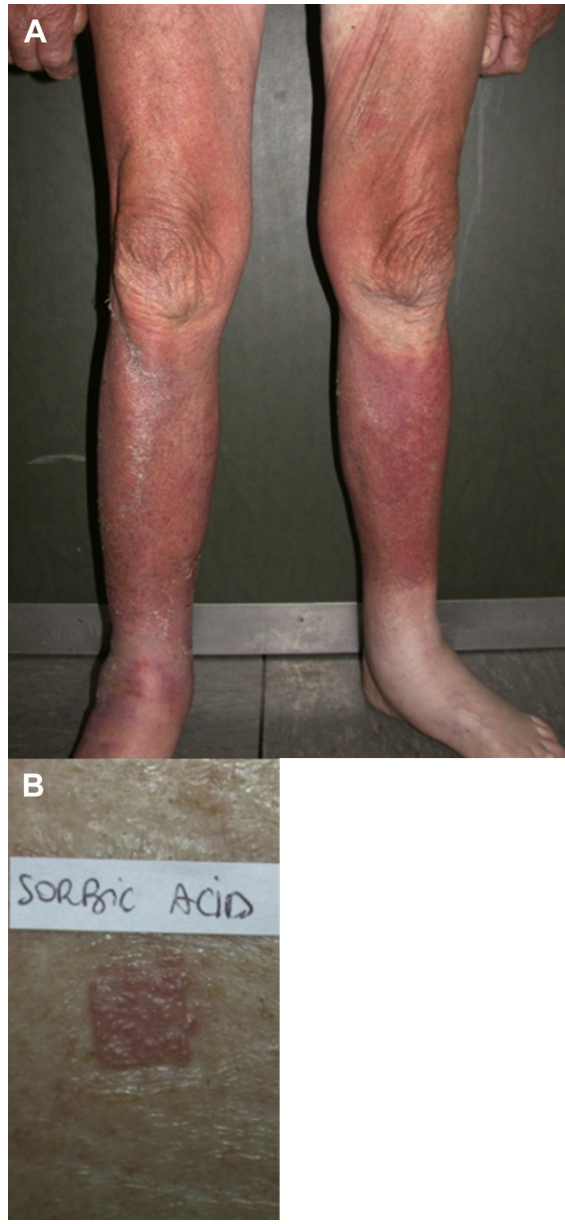


Fig. 3. (*A*, *B*) Allergic contact dermatitis from a combination preparation containing a local antibiotic and corticosteroid due to the preservative potassium sorbate (sorbic acid also positive).

upper back of the patients during 2 days. The readings of the test results are performed about 20 minutes after removal of the patches and again after 3 or 4 days (sometimes later). Allergen identification for a patient with a possible contact allergy to topical pharmaceutical products is performed by means of patch testing with the



Fig. 4. Allergic contact dermatitis from fragrance components, including lavender oil in a nonsteroidal anti-inflammatory product.

standard series, specific pharmaceutical series, the product itself, and all of its ingredients. Sometimes dilution series are used to detect the sensitivity level of the patient and to determine the relevance with regard to the actual use situation.

Open and Semiopen (or Semiocclusive) Tests

These tests are useful modifications for topical pharmaceutical products that have an irritation potential. With an open test, the substance is applied uncovered on the upper arm or upper back twice a day during at least 2 days (without washing the test site).

A semiocclusive test consists of 1 application, with a cotton swab on about 1 cm^2 of the upper back, of a minute amount of a test material, which is left to dry completely, and covered with acrylate paper tape. The readings are performed after 2, 3, or 4 days. Diluted products (eg, 1%–2% aqueous) can also be tested this way.[10]

Use Tests and ROATs

Patch tests are vastly different from normal use conditions; therefore, tests can be completed by provocative use testing of sensitized subjects.[11,12]

With ROATs, about 0.1 mL of test material is applied twice daily to the flexor aspect of the forearm near the cubital fossa, to an area approximately 5 $\times$ 5 cm. The results are read after 1 week, but sometimes ROATs need to be performed up to 21 days, especially with low-concentrated allergens, in order to reveal an allergic reaction.

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