

Contact anaphylaxis after application of an herbal ointment containing phenonip

Key words
anaphylaxis –
phenonip –
phenoxyethanol
– urticaria

Background

Contact urticaria und contact urticaria syndrome are characterized by the immediate development of itchy flares and wheals [1]. Contact urticaria may turn into contact anaphylaxis and may occur after topical application of cosmetics, medical ointments, hair dyes, fresh food, metals, and occupational substances such as cow dander, natural rubber latex, or flour, grains, and feed [1, 2]. Contact anaphylaxis as a form of hypersensitivity reaction is rare but may represent a medical emergency. Epidemiological data for contact anaphylaxis are limited and based on single case reports or small case series. Possibly, these reactions occur more often than estimated. The pathomechanism underlying contact urticaria syndrome and contact anaphylaxis can be IgE-mediated, but most forms seem to results from non-immunological reactions due to the release of vaso-genic mediators [1]. Atopy seems to be a relevant risk factor for the development of contact urticaria, contact urticarial syndrome, and contact anaphylaxis [1].

Case presentation

We report the case of a 10-year-old boy who developed an anaphylactic reaction after topical application of an herbal ointment. The ointment (Kytta® Balsam, Merck Self Medication, Darmstadt, Germany) had been applied for aching muscles on the back. Just a few minutes after application he developed an urticarial skin reaction on the whole back attended and followed by abdominal pain, generalized urticaria, shivering, numbness, dyspnoe, and twitching of the eyelids. Emergency treatment was performed and high-dose corticosteroids and antihistamines were administrated. This led to complete remission of systemic symptoms within two hours and remission of the urticarial skin reaction within 48 hours.

Medical history for allergic or atopic diseases was negative. The patient denied ever suffering from hay fever, asthma, or atopic eczema.

Skin prick testing was performed using a test kit for patch testing that included all ingredients of the ointment (Tab. 1). Due to patent protection, complete information on individual ingredient concentration of the whole product or of „perfume oil special“ was not available. The test kit was provided by the manufacturer (Merck Self Medication, Darmstadt, Germany). Urticarial reactions were seen after two minutes in the whole ointment and phenonip test areas (Fig. 1).

Further prick tests including common aeroallergens (grass, tree, and herbal pollen, house dust mites, and cat epithelia; by Bencard® Allergie GmbH, Munich, Germany) were negative. Skin prick testing with a paraben mixture (16% paraben mix in petrolatum, for patch testing; by Almirall Hermal GmbH, Reinbek, Germany) and further preservatives (sodium sulphite 1%, nipagine 0.1%, nipasol 0.025%, benzoic acid 0.1%, benzyl alcohol 1%, chlorbutanol 0.005%; all diluted in sterile 0.9% sodium chloride solution) and skin prick testing with different concentrations of phenoxyethanol in

Tab. 1 Ingredients of the test kit provided by the manufacturer (Merck Self Medication, Darmstadt, Germany). Due to patent protection, test concentrations were only available for phenonip and methyl nicotinate.

Phenonip 0.37 %	in petrolatum
Lavender oil	in petrolatum
Kytta® Balsam	pure
Cetylstearyl alcohol	in petrolatum
Peanut oil	in petrolatum
Comfrey root fluid	in petrolatum
Petrolatum	pure
Methyl nicotinate 1.2 %	in petrolatum
Eucalyptus oil	in petrolatum
Perfume oil special	in petrolatum
Sodium lauryl sulfate	in petrolatum
Glycerolmonostearate	in petrolatum
Pine needle oil	in petrolatum

Abbreviations

fMLP	N-formyl-methionyl-leucyl-phenylalanine
HSA	human serum albumin
parabens	para-hydroxybenzoic acid

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Fig. 1: Skin prick testing with a test kit containing all single ingredients of Kytta® Balsam (kindly provided from Merck Self Medication, Darmstadt, Germany). Urticarial reactions were observed two minutes after application and prick testing of the substances at the application sites of phenonip (1) and the whole ointment (Kytta Balsam®, 3).

sterile 0.9 % sodium chloride solution (0.01 %, 0.1 % and 1.0 %) were negative as well.

Blood analysis showed normal values for total IgE (18 U/ml) and serum tryptase (11.1 µg/l and 7.4 µg/l, measured at two different time points). IgE mediated basophil response was evaluated in a basophil activation test with phenonip and phenoxyethanol using a broad dose range (1.1 mg/ml – 1.1 ng/ml). Toxic effects were excluded by stimulating basophils with anti-FcεRI in the presence or absence of phenonip or phenoxyethanol at different concentrations.

Activation of basophils by anti-FcεRI and N-formyl-methionyl-leucyl-phenylalanine (fMLP) was as expected (71.3 % ± 2.2 for anti-FcεRI and 66.7 % ± 4.7 for fMLP). In contrast, none of the tested phenonip and phenoxyethanol concentrations induced significant basophil activation, nor did they inhibit the anti-FcεRI induced activation. To address whether hapten binding was required, both substances were pre-incubated either with patient's serum or with human serum albumin

(HSA) for 30 min at 37 °C, prior to use in the basophil activation test. Again, no basophil activation was observed using patient's serum or HSA haptenized with either phenonip or phenoxyethanol over the entire dose range.

Finally, an experimental ImmunoCAP assay to detect specific IgE against phenoxypropionic acid, which contains the phenoxy epitope and a short propionic acid linker (kindly performed by Phadia, Uppsala, Sweden) was also negative.

Conclusion

Phenonip is a broad spectrum antimicrobial agent comprising a synergistic blend of esters of para-hydroxybenzoic acid (parabens) in phenoxyethanol designed for preservation of a wide range of cosmetics and toiletries. It is incorporated in concentrations from 0.25 % to 1.0 % and acts against gram-negative and gram-positive bacteria, yeasts, and moulds. It retains its activity in a broad spectrum of pH values between 3.0–8.0 and is highly stable even after autoclave sterilisation. Furthermore, phenonip can frequently be found in ink pens and in medical vaccines. In general, an allergic reaction against phenonip may result either from an allergy or intolerance reaction against phenoxyethanol or the parabens in this product.

The test kit provided by the manufacturer led to a positive reaction in skin prick testing of the whole ointment and of its ingredient phenonip. However, skin prick testing with parabens and phenoxyethanol in different concentrations was negative. One can only speculate about the cause of these different results, possibly the character of the test vehicle had an influence on the results and only the mixture of parabens and phenoxyethanol in a fatty vehicle led to positive results in skin prick testing. Due to negative results in the basophil activation assay and the experimental ImmunoCAP assay an IgE-mediated allergy seems to be ruled out. This goes in line with the observation that most forms of contact urticaria syndrome or contact anaphylaxis are non-immunological forms and not IgE-mediated [1].

In general, allergic reactions against phenoxyethanol present as late type allergies or allergic contact eczema. Systemic reactions have only been rarely reported. There are few reports on contact urticaria with or without anaphylaxis due to phenoxyethanol [3–7]. In these cases, phenoxyethanol was an ingredient of cosmetics, such as moisturisers, body lotions, or aftershaves.

The first case of a contact anaphylaxis was reported by Ring and colleagues in 1986 [8.] They observed a young woman suffering from contact anaphylaxis after application of an ointment against rheumatism. Emulgade F could be identified as elicitor. It is remarkable that this ointment

contained benzyl nicotinate to increase blood circulation in the skin. In our case, Kytta® Balsam contained methyl nicotinate, which leads to the same effect. Possibly, this mode of action of nicotinic acids promoted a higher grade of anaphylactic reaction in both cases.

We advised our patient to avoid cosmetics that contain phenonip or phenoxyethanol. Furthermore, as many medical vaccines contain phenoxyethanol as a preservative we recommended to avoid vaccines containing phenoxyethanol since it is unclear how he would tolerate these.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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References

1. Gimenez-Arnau A, Maurer M, De La Cuadra J, Maibach H. Immediate contact skin reactions, an update of Contact Urticaria, Contact Urticaria Syndrome and Protein Contact Dermatitis -- „A Never Ending Story“. *Eur J Dermatol* 2010; 20:552–62
2. Gomulka K, Panaszek B. Contact urticaria syndrome caused by haptens. *Postepy Dermatol Alergol* 2014;31:108–12
3. Birnie AJ, English JS. 2-phenoxyethanol-induced contact urticaria. *Contact Dermatitis* 2006;54:349
4. Bohn S, Bircher AJ. Phenoxyethanol-induced urticaria. *Allergy* 2001;56:922–3
5. Hernandez B, Ortiz-Frutos FJ, Garcia M, Palencia S, Garcia MC, Iglesias L. Contact urticaria from 2-phenoxyethanol. *Contact Dermatitis* 2002;47:54
6. Lujan D, Hernandez-Machin B, Penate Y, Borrego L. Contact urticaria due to phenoxyethanol in an aftershave. *Dermatitis* 2009;20:E10
7. Nunez Orjales R, Carballas Vazquez C, Carballada Gonzalez F, Boquete Paris M. 2-phenoxyethanol-induced contact urticaria and anaphylaxis. *J Investig Allergol Clin Immunol* 2010;20:354–5
8. Ring J, Galosi A, Przybilla B. Contact anaphylaxis from emulgade F. *Contact Dermatitis* 1986;15:49–50.