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Case Report

A Hidden Allergen, 3-Dimethylamino-1-Propylamine (DMAPA)

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ABSTRACT

Contact dermatitis of the eyelids was diagnosed by evidence of sensitization to a residual impurity following the manufacture of a cationic surfactant from the amidoamine family, cocamidopropyl dimethylamine, rarely used in the cosmetics industry. On the basis of this clinical case, we propose to analyse the synthesis process of this ingredient, the impurities that may be associated with it and the risks of cross-allergenic reactions between surfactants.

Keywords: Contact eczema; Sensitisation; Cosmetics; Cocamidopropyl dimethylamine

INTRODUCTION

Surfactants are essential ingredients in cosmetics, generally for their emulsifying properties, but also in some personal care products for their detergent and foaming properties or as conditioning agents. During the various stages of their manufacture, surfactants may be contaminated with impurities, including 3-Dimethylamino-1-Propylamine (DMAPA), which has allergenic potential. This unintentional contamination can cause contact eczema, particularly on the scalp and eyelids.

CASE PRESENTATION

We present the case of a young patient of 18 years of age with no medical or surgical history and no long-term treatment. The patient has a personal atopic background, suffering from atopic dermatitis since early childhood, with the appearance of wrinkles predominant since adolescence.

Since August, 2023 the patient reports the onset of facial eczema with predominant symmetrical eyelid involvement (Figures 1A and 1B). The eczematous lesions on the rest of the body did not worsen, with always symmetrical involvement of the folds. The patient had tried several treatments: Antihistamine eye drops, antihistamine per os and a mid-range dermocorticoid. But each time the dermocorticoids were stopped, the palpebral lesions systematically recurred.

An allergological investigation was carried out at the Strasbourg Dermato-allergology Unit using a standard European battery supplemented by patch testing with products brought by the patient. The 48 and 72 h results were positive for colophony, 3-Dimethylamino-1-Propylamine (DMAPA) and two cosmetics brought by the patient, namely Ordinary® Anti-Serum salicylic Acid Imperfections 2% and l'Oréal® Magic CC cream anti-red skin conditioner (Figure 2). The product compositions are shown in Table 1. These two products were the only cosmetics the patient had used on her face for many months. Rosin is a resin derived from pine trees, and is widely used in cosmetics, adhesives and the wood industry. The allergy is mainly caused by rosin oxidation products, which are the main allergens. The prevalence of this allergy varies according to population and occupation, with higher exposure in sectors such as cosmetics. In this patient, the positive test may reflect a sensitization, which is not clinically relevant at this stage since there is no rosin in the products currently used by the patient [1].

We obtained from the L'Oréal laboratory samples of each component that could be tested separately in patch tests with readings at 48 and 72 h: The patch tests were negative for the different component but positive for the finished product located in 26 (Figure 3). The samples tested may not have been in sufficient concentration, or the combination with other cosmetics used by the patient may be responsible for an irritating phenomenon. Looking at the composition of Ordinary® serum, we rank 3rd in the list of ingredients for cocamidopropyl dimethylamine, a surfactant used for its antistatic, emulsifying and foaming properties. This surfactant requires the addition of DMAPA in its manufacturing process, a molecule to which our patient is allergic.

In our case, we believe that the Ordinary® serum is at the origin of the palpebral eczema *via* DMAPA, an impurity of cocamidopropyl dimethylamine. After the patient stopped using this cosmetic product, the lesions healed and did not recur.

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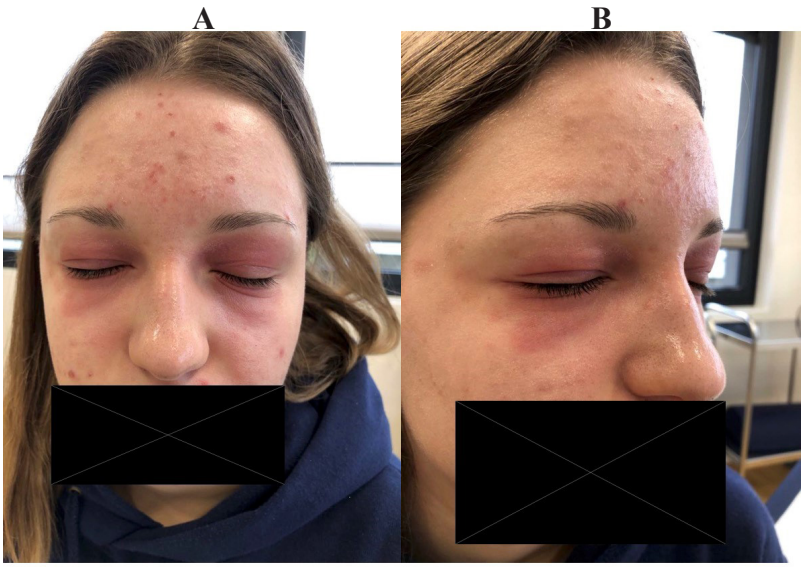

Figure 1: Clinical examination of the patient. **Note:** A) Symmetrical eyelid involvement; B) Lesions on the folds of the arms.

Batterie standard EECDRG (2000) et ICDRG (1997). Modification 27/11/2017

Allergènes	%	20'	48h	72h	96h		Pertinence
1. D ichromate de potassium vas.	0,5						
2. Neomycin sulfate vas.	20						
3. Thiuram mix vas.	1						
4. Fragrance mix II vas.	14						
5. Cobalt(II)chloride hexahydrate vas.	1						
6. *p*-Phénylènediamine base (PPD) vas.	1						
7. Methyliso +methylchloroisothiazolinone aq.	0,02						
8. Formaldéhyde *(aq.)*	2						
9. Colophonium vas.	20		+	++			
10. Clioquinol vas.	5						
11. Peru balsam	25						
12. N-isopropyl-N-phényl-4-phenylenediamine vas.	0,1						
13. Lanolin alcohol vas.	30						
14. Epoxy resin, Bisphenol A vas.	1						
15. Mercapto mix vas.	2						
16. Budésonide vas.	0,01						
17. Paraben mix vas.	16						
18. 4--*tert*-butylphénolformaldéhyde resin vas.	1						
19. Fragrance mix I vas.	8						
20. Quaternium-15 vas.	1						
21. Nickel(II)sulfate hexahydrate vas.	5						
22. Benzocaine vas.	5						
23. 2-Mercaptobenzothiazole vas.	2						
24. Sesquiterpene lactone mix vas.	0,1						
25. Tixocortol-21-pivalate vas.	0,1						
26. Methyldibromo glutaronitrile vas.	0,5						
27. Primine(2methoxy-6-n-pentyl-4-benzoquinone)	0,01						

Ajouts du service (au 1er.09.2009)

28. Lyral® vas	5						
29. Hydrocortisone-17-butyrate vas.	1						
30. Amerchol® L- 101 vas.	50						
31. 3-(Diméthylamino)-1-propylamine aq.	1		+	++			
32. Disperse blue 106 vas.	1						
33. Benzalkonium chloride aq.	0,1						
34. Propylène glycol *(aq.)*	5						
35. Imidazolidinyl urea vas.	2						
36. Triclosan vas.	2						
37. Iodopropynyl butylcarbamate vas.	0,2						
38. Cetearyl alcohol vas.	20						
39. Vaseline blanche							Témoin -
40. Lauryl sulfate de sodium *(aq.)*	0,25						Témoin IR
41. 1,3 Diphénylguanidine vas.	1						
42. Méthylisothiazolinone (aq.)	0,2						
43. D-Limonene vas.	10						
44. Bisphénol A vas.	1						
45. Linalool vas.	10						

Figure 2: European standard battery patch test results.

Table 1: Cosmetic ingredient lists provided by patient and positive patch tests.

The Ordinary® sérum anti-imperfections acide salicylique 2%	L'Oréal® Magic CC Cream embellisseur de teint anti-rougeurs
Aqua (water), Saccharide isomerate, Cocamidopropyl dimethylamine, Salicylic acid, Hydroxyethylcellulose Polysorbate 20, Citric acid, Sodium citrate, Sodium hydroxide, Phenixyethanol, Chlorphenesin	Aqua (water), Isododecane, Dimethicone, Isohexadecane, Glycerin, PEG-10 dimethicone methyl methacrylate crosspolymer, Butylene glycol, Titanium dioxide (nano)/titanium dioxide, Pentylene glycol, Disteardimonium hectorite, Panthenol, Phenoxyethanol, Cetyl peg/ppg-10/1 dimethicone, Acrylates/ammonium methacrylate copolymer, Sodium chloride, Polyglyceryl-4 isostearate, Hexyl laurate, Boron nitride, Caprylyl glycol, Parfum (Fragrance), Triethyl citrate, stearic acid, aluminum hydroxide Tocopherol, Synthetic fluorphlogopite, Disodium stearoyl glutamate, Pentaerythrityl tetra-di-t-butyl hydroxyhydrocinnamate

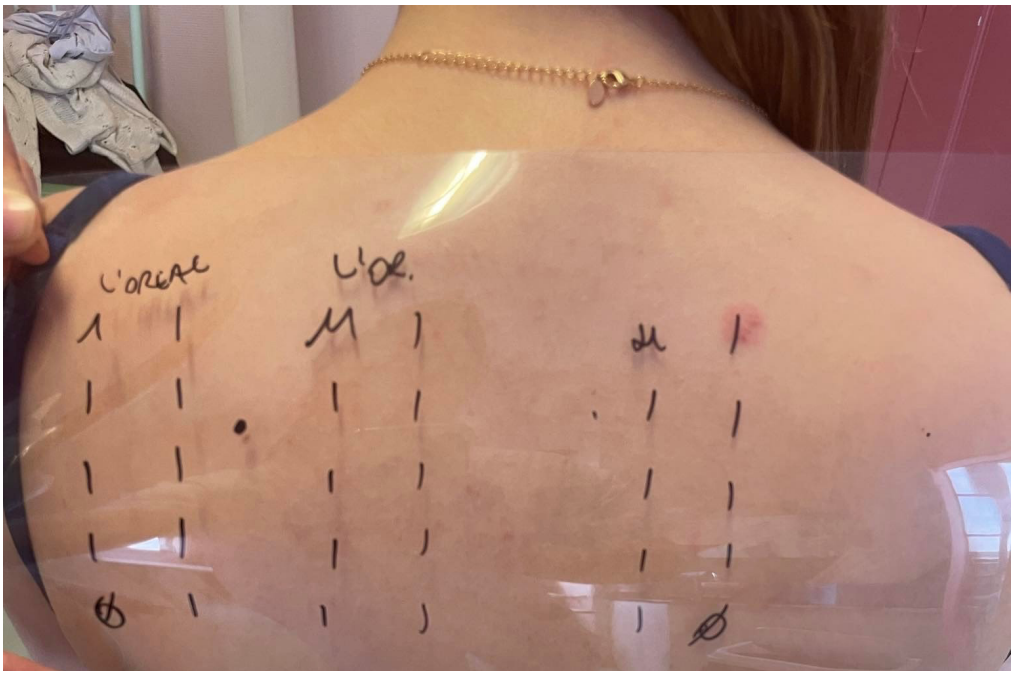

Figure 3: Results obtained with the different L'Oréal cream® components. The number 26 that is positive is the final product.

RESULTS AND DISCUSSION

DMAPA is commonly found in cleansing products such as personal care products (shower gels, liquid soaps and detergents, make-up removers and contact lens solutions) [2]. This inexpensive reagent enables excellent yields to be achieved in chemical reactions, without the need for chromatographic purification. Given the low cost and usefulness of DMAPA, this laboratory chemical is likely to be increasingly used to facilitate reaction preparation procedures in organic chemistry [3].

In fact, this molecule is used in the synthesis of several surfactants such as Cocamidopropyl Betaine (CAPB), which is also widely used. The process of synthesising these molecules involves several steps. First, DMAPA is reacted with the fatty acid in coconut oil to form an intermediate, cocamidopropyl dimethylamine, also known as Amidoamine (AA). The second step is betainisation: The AA intermediate cocamidopropyl dimethylamine then reacts with chloroacetic acid to form Cocamidopropyl Betaine (CAPB) [2].

While cocamidopropyl betaine is particularly popular for its sweetness and ability to create rich lather, cocamidopropyl dimethylamine is mainly used for its conditioning and emulsifying properties. This is because the former is an anionic surfactant, while the latter is cationic. Cationization with DMAPA produces modifications that do not denature proteins but allow a variety of biomaterials to be assembled into highly complex hierarchical structures, and to retain or enhance their functionality in conditions where their original structure would be compromised [4].

Initially, the use of CAPB was promoted because of its low irritancy and presumed hypoallergenicity. However, in the 1980s, cases of contact allergy to CAPB were reported. Studies then showed that most allergic reactions to CAPB were actually due to contamination with DMAPA: Commercial CAPB was contaminated by this reagent used in its synthesis and could contain up to 3.0% 3-dimethylamino-1-propylamine and up to 0.02% DMAPA [2]. CAPB is primarily an irritant and should not be considered a significant contact allergen according to several authors [2,3]. For example, in the retrospective analysis of patch test results for CAPB in 1% aqueous solution in water collected by the Information Network of the Departments of Dermatology from 1996 to 2009, of the 83,864 patients tested, 2.16% reacted positively to CAPB compared with 4.6% of irritant reactions [5]. Another study conducted between 2002 and 2009 on 1,092 patients who had patch tests for CAPB and its impurities reported a high percentage of irritating reactions (39% of the patients) while only 15 patients (1.3%) developed allergic reactions: 13 to cocamidopropyl dimethylamine, 11 to DMAPA, 8 to Oleamidopropyl Dimethylamine (OPD) and 2 to CAPB [6].

Despite the rare occurrence of true allergic reactions to BPAC, it is the impurities in commercial BCAP, such as cocamidopropyl dimethylamine and DMAPA, that are the real sensitisers. There is still some debate about the responsibility of DMAPA or cocamidopropyl dimethylamine as the impurity responsible for the true allergenic power of CAPB. For some authors it is DMAPA that is responsible for allergic reactions to both cocamidopropyl dimethylamine and CAPB, while for others cocamidopropyl dimethylamine has its own allergenic properties [7,8]. Fowler et al., reported a series of 9 patients who were allergic to CAPB-containing products [8]. Six of these had positive patch tests for cocamidopropyl dimethylamine (1% aqueous solution) but none for DMAPA (1% pet) or CAPB free of traces of cocamidopropyl dimethylamine. However, it is not clear whether the cocamidopropyl dimethylamine used in the patch tests was free of DMAPA-type impurities. According to Foti et al., the real allergen would be DMAPA. However, the real allergen, but its penetration into the skin is more easily done *via* cocamidopropyl dimethylamine, which is then degraded *in vivo* into DMAPA during an enzymatic hydrolysis reaction, operation inverse of the first stage of synthesis of CAPB [7]. In the patient whose serum was negative to cocamidopropyl dimethylamine but positive to DMAPA from our standard battery, we believe that the impurities in DMAPA are responsible for the allergic contact dermatitis observed. Moreover, the patient's atopic background may have contributed to her sensitization to CAPB impurities, as suggested in the article by Collis RW who concluded that CAPB-containing products should be avoided in paediatric care products, especially as children suffer from atopic dermatitis [9].

Non-occupational exposure to BPAC and its impurities, DMAPA and cocamidopropyl dimethylamine, is mainly *via* cosmetics (here a patient serum), including mainly rinsing hygiene products such as liquid soaps, shampoos or conditioners, but also permanent solutions, deodorants, sanitary wipes, make-up removers, bubble baths and toothpastes [2,5]. Given the nature of the exposure sources, the face and scalp are typical sites for non-professional contact eczema to surfactants. Due to the fineness of the skin on the eyelids, there is an increased risk of irritative and allergic contact reactions to DMAPA and other surfactants for this site, even at low concentrations. We found a clinical case published in 2008 similar to our patient. After patch testing, this patient was found to be sensitised to DMAPA from a shampoo. The patient achieved a complete and sustained remission of her dermatitis after avoiding all products containing DMAPA and CAPB. Occupational exposure to DMAPA may occur less frequently, for example through the use of shampoos and liquid soaps by nurses and nursing assistants or hairdressers, or while working in detergent manufacturing plants containing CAPB [6]. These are mainly occupational allergies, hand eczema and almost always associated irritants and sometimes other contact allergens [6]. Regarding the risk of cross-reactivity, more than ten thousand patients were tested for CAPB, cocamidopropyl dimethylamine, DMAPA, Oleamidopropyl Dimethylamine (OPD) and Cocamide Diethanolamide (CDEA) between 2009 and 2014: OPD showed the highest positivity rate (2.3%), followed by DMAPA (1.7%) and CAPB (1.4%) *versus* cocamidopropyl dimethylamine and CDEA (0.8%) [10]. This study concluded that there is a risk of cross-reactivity between several surfactants, including CAPB, cocamidopropyl dimethylamine, DMAPA and OPD, with CAPB-positive patients being much more likely to react to other surfactants and AECB being least likely to interact with others. For the latter, which is structurally different from other surfactant molecules, it is likely to be co-sensitisation rather than true cross-reactivity [10]. In addition, DMAPA and cocamidopropyl dimethylamine are starting materials for the synthesis reaction and may be residual impurities in the ingredient. Thus, structural similarities or the presence of common impurities may explain these co-reactivities [10].

CONCLUSION

Allergy to 3-(Dimethylamine)Propylamine (DMAPA) can cause allergic dermatitis of the face, particularly the eyelids and scalp. This means being able to analyse the International Nomenclature Cosmetic Ingredient (INCI) list of cosmetic products to think about potential contaminants and include them in our patch tests. Many products contain DMAPA unintentionally because it is an impurity found in products containing Cocamidopropyl Betaine (CAPB), oleamidopropyl dimethylamine or cocamidopropyl dimethylamine.

CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest.

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