

Eyelid Dermatitis: Contact Allergy to 3-(Dimethylamino)propylamine

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We present the case of a 42-year-old woman with intractable eyelid dermatitis. Patch testing revealed sensitization to 3-(dimethylamino)propylamine (DMAPA). DMAPA is an important etiology of allergic contact dermatitis of the eyelids and face but is easily missed even with expanded-series patch testing. We also review the most common causative allergens in eyelid dermatitis cited in the literature over the past decade. DMAPA is a reagent used in the formation of cocamidopropyl betaine (CAPB), a common additive to liquid soaps, shampoos, and other cleansing products because of its utility as a surfactant. Beginning in the 1980s, reports of allergy to CAPB surfaced in the literature. Ultimately, a majority of patch testing studies have shown that clinical allergy to CAPB-containing products actually reflects allergy to contaminant DMAPA in most cases. Amidoamine, another intermediate in the formation of CAPB, may also be implicated through a proposed mechanism of conversion to DMAPA in the skin. When patch-testing for eyelid and facial dermatitis, it is crucial to test with DMAPA directly, not just with CAPB; unlike commercial-grade CAPB, the CAPB in patch test kits is ultrapure and does not contain contaminant DMAPA.

THERE has been much debate in the literature and at scientific gatherings in the recent past regarding the allergenicity of the surfactant cocamidopropyl betaine (CAPB) and the primary contaminants found in its commercial-grade preparations, namely, 3-(dimethylamino)propylamine (DMAPA) and amidoamine. We present a case that supports DMAPA as the primary allergen. We also examine this allergen in the context of the other compounds most commonly cited as causing eyelid dermatitis in the literature over the past 10 years.

Case Report

A 42-year-old woman presented for evaluation with a 4-month history of severe recalcitrant eyelid dermatitis. She had previously discontinued all eye makeup, without benefit. She could not tolerate treatment with either topical corticosteroids or calcineurin inhibitors because of a burning sensation on application. She had also been given three separate tapers of systemic corticosteroids;

each of these provided only temporary resolution of her dermatitis. On presentation, she had bilateral periorbital and postauricular erythema (Fig 1). A biopsy specimen showed spongiotic dermatitis. Patch testing was performed with a comprehensive cosmetic series and a modified North American Contact Dermatitis Group standard series with IQ Chambers (Chemotechnique Diagnostics, Malmö, Sweden). Readings were performed on days 2 and 4. On day 4, there was a + reaction to DMAPA 1% aqueous (obtained from Chemotechnique) as well as a + reaction to neomycin and a +++ reaction to bacitracin, consistent with the patient's history of allergy to topical antibiotics. There were no reactions to either CAPB or amidoamine. Treatment included open wet dressings followed by application of hydrocortisone probutate cream and avoidance of all DMAPA- and CAPB-containing products (most notably her shampoo, which contained CAPB). By following these instructions, she has had a complete and sustained resolution of her dermatitis for 11 months.

Discussion

DMAPA is a reagent used in the formation of the amphoteric surfactant CAPB (Fig 2). The process begins with the addition of coconut fatty acids to DMAPA to form the intermediate compound, amidoamine. Amidoamine is then combined with monochloroacetic acid to form CAPB, the final product.

Because of its usefulness as a foaming agent, CAPB is found in myriad personal care products such as shampoos,

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Figure 1. Bilateral periorbital and postauricular erythema.

body washes, liquid soaps and detergents, makeup removers, and contact lens cleaners. It was initially promoted for widespread use because of its purported low irritancy and hypoallergenicity; in 1983, however, case reports of contact allergy to CAPB began to appear.¹⁻³ Recognition of allergy to CAPB-containing products became so prevalent that CAPB was named Contact Allergen of the Year in 2004 by the American Contact Dermatitis Society. A body of evidence in the literature now supports the contention that CAPB is in fact not the responsible chemical in the vast majority of these cases.

Commercial-grade CAPB is contaminated with the reagents used in its formation and can contain up to 3.0% amidoamine (the intermediate product) and up to 0.02% DMAPA.⁴ The bulk of the literature now contends that DMAPA is the responsible allergen in cases of contact dermatitis from CAPB-containing products. Investigational patch testing by Angelini and colleagues revealed that a group of 30 patients with a clinical history of dermatitis from products containing CAPB and positive patch-test reactions to commercial-grade CAPB (contain-

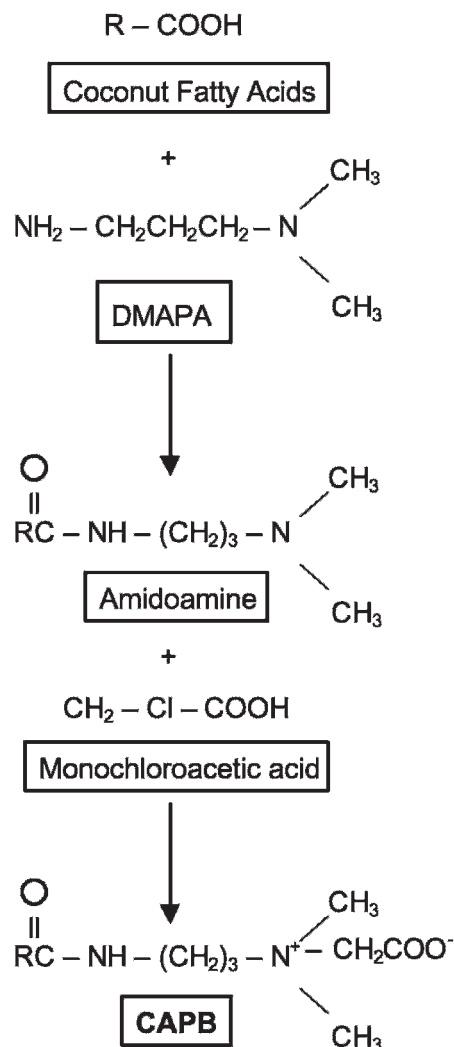


Figure 2. Synthesis of cocamidopropyl betaine (CAPB). (DMAPA = 3-(dimethylamino)propylamine.)

ing contaminant DMAPA and amidoamine) all had positive patch-test reactions to DMAPA.⁵ However, when tested with scientific-grade CAPB, which is purified to the point that levels of DMAPA are undetectable, none of the patients had a positive reaction nor did they have positive reactions to sodium chloride or N,N-dimethyl-propylene-diaminotriacetic acid, other impurities present in commercial-grade CAPB. Similar findings have been made in other studies and case reports.⁶⁻⁹

There has been much discussion in the literature regarding the primacy of DMAPA versus amidoamine as the contaminant in CAPB that causes allergic contact dermatitis. Some investigation groups favor amidoamine as the primary allergen¹⁰; Fowler and colleagues cited 6 of 9 cases in which patients with allergy to products

containing CAPB had positive patch-test reactions to amidoamine but not to DMAPA.¹¹ However, it is not clear that purified samples of amidoamine (not containing DMAPA) were used in these experiments; further, Angelini and Rigano questioned whether the concentration of DMAPA tested was high enough to elicit a positive reaction.¹² To investigate this controversy directly, Foti and colleagues patch-tested 10 patients who had contact allergy to commercial-grade CAPB with DMAPA and with various concentrations of pure amidoamine.¹³ All patients had positive reactions to DMAPA, negative reactions to purified CAPB, and positive reactions to 0.5% and 0.25% aqueous solutions of amidoamine. Only four patients had positive reactions to amidoamine at a lesser concentration of 0.1% aqueous.

One theory that could explain these graded results is the concept of *in situ* enzymatic hydrolysis of amidoamine.¹³ Amidoamine is an amphiphilic compound that is readily absorbed by the skin and has an affinity for keratinocytes. Enzymatic hydrolysis at the amide bond (Fig 3) could release coconut fatty acid and the allergenic DMAPA directly into the skin; this reaction is simply a reversal of the first step in the formation of CAPB (see Fig 2). The allergic response to the DMAPA released in this manner could vary from case to case depending on the concentration of amidoamine, the amount of enzymatic hydrolysis effectively taking place, the integrity of an individual's epidermis, and the type of carrier in which it is dissolved.

This last factor, known as the carrier effect, is another means by which increased levels of DMAPA might access the skin. The principle of the carrier effect states that the allergenicity of DMAPA is modified by its carrier. Angelini and colleagues showed that DMAPA is allergenic at lower

concentrations when dissolved in CAPB or sodium lauryl ether sulfate (SLES) as compared to the same amount dissolved in lauryl polyglucoside.^{6,14} This is likely due to the greater irritancy potential of SLES, a carrier that is commonly paired with CAPB in commercial detergent systems.

Angelini and colleagues analyzed the chemical structure and sensitizing properties of DMAPA and similarly structured compounds.⁶ They found that the presence of two amino groups (one of which is tertiary and dimethyl substituted, separated by either two or three carbon atoms) is necessary to elicit an allergic reaction in DMAPA-sensitive persons. The amino groups in DMAPA are separated by three carbon atoms. Angelini and colleagues posited that this combination of features, creating an asymmetric molecule with a propensity to form a ring structure including a chemically reactive tertiary amine, is characteristic of allergenic compounds.⁶

To date in the literature, there are at least 61 separate reported cases of contact allergy attributed to DMAPA.^{4,8,9,15-18} The potential sources and types of exposure to DMAPA are many. The bulk of reported cases of sensitization to DMAPA is via non-occupational exposure to detergent systems containing CAPB. Occupational sensitization to DMAPA as a contaminant in shampoos and soaps has been reported in health care workers, including a nurse whose responsibilities included washing the hair of patients with their own shampoos.⁸ Occupational sensitization has also been reported in chemical factories where DMAPA was being used to produce CAPB.¹⁶ DMAPA can also be found in the production of fuels, pesticides, flocculants, ion exchangers, and dyes and is used as an epoxy resin hardener.^{6,19} Oleamidopropyl dimethylamine is a surfactant that is similar to CAPB in that it also requires DMAPA as a reagent in its formation and therefore contains residual unreacted substrate in the final product.¹⁵ However, it is not commonly used in the United States.

DMAPA is only one of the many chemical agents that have been reported to cause allergic contact eyelid dermatitis. Throughout the years, women have consistently been affected by allergic contact eyelid dermatitis much more frequently than men (most series are at least 80% female),²⁰⁻²⁵ a reflection of the greater use of hair care and face care products among women. The changing patterns of the most common allergens over the years reflects our increasing knowledge of potential allergens and our ability to test for them, as well as the changing palette of chemicals and products available for use by industry.

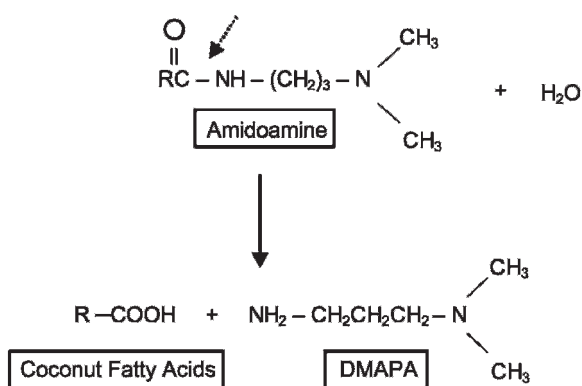


Figure 3. Enzymatic hydrolysis of amidoamine via cleavage of the amide bond, indicated by the dashed arrow. (DMAPA = 3-(dimethylamino)propylamine.)

Table 1 lists the most common compounds causing allergic contact eyelid dermatitis, as culled from the last decade of literature on eyelid dermatitis.^{26–31} Given the thinness of the skin, eyelids are particularly susceptible to irritant and allergic contact reactions. This is one reason why low-level contaminants such as DMAPA in a wash-off product can still be an important cause of allergic contact eyelid dermatitis. Other commonly cited causes are metals such as gold, nickel, cobalt, and chromate, which can be present in makeup such as eye shadow or in metal appliances such as eyelash curlers or tweezers. Antibiotics and eye medications, most notably those containing aminoglycosides, are frequent causes of dermatitis around the eyes. Personal care products, including shampoos, fragrances, face creams, makeup, sponge applicators and brushes, botanicals, and vitamin oils, are often cited. Some of the more frequently recognized allergenic additives to these kinds of products include fragrance mix, balsam of Peru, and cinnamic aldehyde. However, in many cases, the specific causative allergen has not been identified. Nail product ingredients, including tosylamide formaldehyde resin (present in varnish), cyanoacrylates, and the methacrylates present in artificial nails, are cited as being responsible in approximately 10% of cases in most series. Additives such as lanolin alcohol and propylene glycol were among the 26 most common causes of allergic eyelid dermatitis as determined from the North American Contact Dermatitis Group's 2003–2004 data.²⁸ Preservatives, including methyldibromoglutaronitrile, quaternium-15, and benzalkonium chloride, are commonly implicated. Protein contactants, including dust mites, animal dander, cornstarch, and latex, are increasingly being recognized, as are corticosteroid allergies. Airborne contactants can settle and accentuate a dermatitis in the periorbital folds.³² Many airborne allergens have been identified,³³ including fragrances, wood dusts, and resins such as colophony. Finally, also represented in the literature are the surfactants CAPB and oleamidopropyl dimethylamine (or perhaps more accurately, their contaminants, DMAPA and amidoamine).

Conclusion

Allergy to 3-(dimethylamine)propylamine (DMAPA) can be an elusive cause of eyelid and facial dermatitis. There are numerous products that contain contaminant DMAPA, including items with cocamidopropyl betaine (CAPB) and oleamidopropyl dimethylamine. The contaminant amidoamine is another potential source of DMAPA via in situ hydrolysis. Sometimes, product bottles

Table 1. Compounds That Have Most Frequently Caused Allergic Contact Eyelid Dermatitis in the Last Decade

Metals

Gold sodium thiosulfate
Nickel sulfate
Cobalt
Potassium dichromate

Eye medications and antibiotics

Aminoglycosides
Gentamicin
Neomycin
Bacitracin
Phenylephrine

Personal care products

Shampoos
Fragrances
Fragrance mix
Balsam of Peru
Cinnamic aldehyde
Face creams
Makeup (especially eye shadow)
Makeup applicators
Sponges (can contain thiuram mix)
Brushes
Botanicals and vitamin oils
Ylang ylang oil
d- α -Tocopherol acetate

Nail products

Tosylamide formaldehyde resin
Cyanoacrylates
Methacrylates

Vehicles and additives

Propylene glycol
Lanolin alcohol

Preservatives

Methyldibromoglutaronitrile
Quaternium-15
Methylchloroisothiazolinone
Dimethylol dimethyl hydantoin
Benzalkonium chloride
Formaldehyde
Sodium disulfite
Kathon CG
Phenylmercuric acetate

Protein contactants

Dust mites
Animal dander
Cornstarch
Latex

Steroids

Tixocortol
Budesonide
Desonide

Table 1. Continued

Airborne contactants

Fragrance mix

Resins

Colophony

Plants

Monoterpenes

Wood dust

Surfactants and related chemicals

3-(dimethylamino)propylamine

Amidoamine

Cocamidopropyl betaine*

Oleamidopropyl dimethylamine

*In most cases, contaminants have not been evaluated.

will list “coconut-derived surfactants,” which can be assumed to contain contaminant DMAPA unless otherwise specified. Patients with confirmed DMAPA allergy should be counseled to avoid all of the above-mentioned products.

When patch-testing patients, it is important to know that the T.R.U.E. Test (Mekos Laboratories A/S, Hillerød, Denmark) does not include DMAPA or CAPB. Specialty test kits that do include CAPB provide ultrapure scientific-grade CAPB and therefore will give a negative result even in the case of true DMAPA allergy. For example, the North American Contact Dermatitis Group obtains its CAPB from Chemotechnique Diagnostics, and this same product was shown to be pure enough not to elicit reactions in known DMAPA-sensitive patients.¹³ For this reason, it is imperative to test with DMAPA directly when investigating head and neck allergic contact dermatitis. Alternative products, including the Free & Clear brand of shampoos, (Pharmaceutical Specialties, Inc., Rochester, MN) are available for DMAPA-allergic patients.

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