

Cutaneous Delayed-Type Hypersensitivity to Surfactants

Joseph F. Fowler, Jr, MD, Cristin N. Shaughnessy, BS, Donald V. Belsito, MD, Joel G. DeKoven, MD, Vincent A. Deleo, MD, Anthony F. Fransway, MD, Howard I. Maibach, MD, James G. Marks, MD, C.G. Toby Mathias, MD, Melanie Pratt, MD, Denis Sasseville, MD, James S. Taylor, MD, Erin M. Warshaw, MD, Matthew J. Zirwas, MD, Kathryn A. Zug, MD, and Douglas Lorenz, PhD

Background: Repeated and prolonged use of surfactants can cause irritant as well as allergic contact dermatitis.

Objective: This study reports the frequency of positive patch test results to surfactants tested on the North American Contact Dermatitis Group screening series including cocamidopropyl betaine (CAPB), amidoamine (AA), dimethylaminopropylamine (DMAPA), oleamidopropyl dimethylamine (OPD), and cocamide diethanolamide (CDEA), and correlations of positive reactions between CAPB and the other surfactants.

Methods: This was a retrospective analysis of 10 877 patients patch tested between 2009 and 2014 to the surfactants CAPB, AA, DMAPA, OPD, and CDEA. Frequencies of positive reactions to these surfactants were calculated, and trends of reactivity between the surfactants analyzed.

Conclusions: The OPD had the highest rate of positive patch reactions (2.3%) followed by DMAPA (1.7%), and CAPB (1.4%). The AA and CDEA had the lowest rate of positive reactions (0.8%). There was a high degree of overlap in positive patch tests between the surfactants. The CDEA was the least likely to coreact with another surfactant.

Cutaneous delayed-type hypersensitivity is a T cell–mediated hypersensitivity response that presents as allergic contact dermatitis (ACD) with a pruritic and eczematous skin reaction.¹ Surfactants are cleansing agents primarily found in personal care products and household cleansing products, such as soaps, shampoos, surface cleaners, and so on. Surfactants can damage the skin and occasionally cause ACD in addition to irritant contact dermatitis.²

The North American Contact Dermatitis Group (NACDG) screening series currently tests the surfactants cocamidopropyl betaine (CAPB), amidoamine (AA), dimethylaminopropylamine (DMAPA), oleamidopropyl dimethylamine (OPD), and cocamide diethanolamide (CDEA) (Fig. 1).^{3,4} The CAPB is formed by reacting fatty acids extracted from coconut oil with DMAPA. This first step yields cocamidopropyl dimethylamine (AA, cocamidoamine), which then

reacts with sodium monochloroacetate to give the end product CAPB.³ Major known impurities of CAPB include low quantities of the starting material DMAPA and the intermediate AA.^{5,6} The OPD results from the reaction of DMAPA and oleic acid.⁷ The CAPB and the OPD share DMAPA as a starting material.

The CAPB has been most commonly reported among the surfactants to cause ACD. There is debate over whether the real allergen in many cases of ACD to CAPB is the chemical itself, or the impurities DMAPA and AA.^{2,5,6,8–10} The OPD is a surfactant found in cosmetics, baby lotions, and body lotions that has been the cause of occasional reports of ACD.^{1,7} The OPD was found in 1 study to be one of the leading causes of allergic eyelid dermatitis.¹¹

The CDEA is a nonionic surfactant used in shampoos, hand gels, liquid soaps, surgical disinfectants, and dishwashing liquids. The CDEA rarely causes ACD and is not structurally related to the CAPB family of surfactants mentioned above.^{2,12,13} Concomitant reactions between CDEA and the other surfactants, therefore, are likely due to coreactivity rather than cross-reactivity.

This study reports the frequency of positive patch test results to surfactants tested on the NACDG screening series including CAPB, AA, DMAPA, OPD, and CDEA and correlations of positive reactions between CAPB and the various other surfactants.

METHODS

This was a retrospective analysis of 10 877 patients evaluated for suspected ACD between 2009 and 2014. All patients were patch

From the University of Louisville School of Medicine, Louisville, KY.

Address correspondence to Cristin N. Shaughnessy, BS, University of Louisville School of Medicine, 2125 Longest Ave, Louisville, KY. E-mail: cristinshaughnessy@gmail.com.

The authors have no funding or conflicts of interest to declare.

Disclaimer: This material is the result of work supported with resources and the use of facilities at the Minneapolis Veterans Affairs Medical Center, USA. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

This work has not been previously presented.

DOI: 10.1097/DER.0000000000000150

© 2015 American Contact Dermatitis Society. All Rights Reserved.

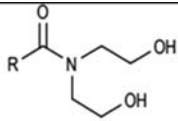
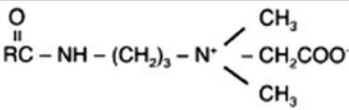
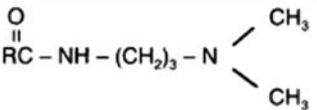
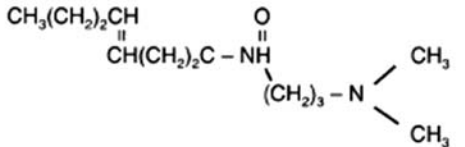
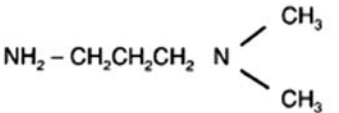
CDEA	
CAPB	
AA	
OPD	
DMAPA	

Figure 1. Chemical structure of CDEA, CAPB, AA, OPD, and DMAPA (R = coconut fatty acids).^{3,4}

tested in a standardized manner to the NACDG series, including CAPB, 1.0% aqueous; AA, 0.1% aqueous; DMAPA, 1.0% aqueous; OPD, 0.1% aqueous; and CDEA, 0.5% petroleum.¹⁴

Frequencies of positive allergic reactions to each surfactant as well as coreactivity to other surfactants were calculated. Odds ratios were calculated for reactivity to AA, DMAPA, OPD, and CDEA for individuals who patch tested positive to CAPB as compared with those who were negative using statistical software (R: A Language and Environment for Statistical Computing; R Foundation for Statistical Computing, Vienna, Austria).

TABLE 1. Final Patch Test Reading for the 5 Surfactants

Final Reading	CAPB	AA	DMAPA	OPD	CDEA
1+	152	86	189	246	91
2+ or 3+	0	0	0	2	1
(+/-)	11	4	14	23	8
Irritant	70	24	22	73	13
Negative	10 644	10 763	10 652	10 533	10 764
Total	10 877	10 877	10 877	10 877	10 877

TABLE 2. Positive Reactions for the 5 Surfactants

	Positive Reactions	%
CAPB	152/10 877	1.4
AA	86/10 877	0.8
DMAPA	189/10 877	1.7
OPD	248/10 877	2.3
CDEA	92/10 877	0.8

RESULTS

Reactions were scored as irritants, questionable (+/-), 1+, 2+, or 3+ (Table 1). Reactions scored as 1+, 2+, or 3+ were included as a positive allergic response. Of the 10 877 patients patch tested, 1.4% (n = 152) patch tested positive to CAPB, 0.8% (n = 86) to AA, 1.7% (n = 189) to DMAPA, 2.3% (n = 248) to OPD, and 0.8% (n = 92) to CDEA (Table 2).

Concomitant reactivity of each surfactant is summarized in Table 3. Among the 152 patients with positive reactions to CAPB, 84 (55%) were positive to CAPB alone, and the following were concomitantly positive to other surfactants: 20 (13%) to AA, 25 (16%) to DMAPA, 46 (30%) to OPD, and 8 (5%) to CDEA (Table 3).

For the related surfactants (CAPB, AA, DMAPA, and OPD), a Venn diagram was constructed to represent the complete cosensitivity of the 4 substances (Fig. 2). Odds ratios for reactivity to AA, DMAPA, OPD, and CDEA between the populations of patients testing positive and negative to CAPB are summarized in Table 4.

DISCUSSION

The OPD had the highest frequency of positive reactions (2.3%) followed by DMAPA (1.7%), and CAPB (1.4%). The AA and CDEA had the lowest frequency of positive reactions of the surfactants (0.8%) (Table 2). Surfactants are marginal irritants, and mild false-positive irritant reactions were seen (Table 1).

The CDEA was the least likely to coreact with the other surfactants. Eighty-five percent (78/92) of the positive allergic reactions to CDEA were unique to CDEA alone (Table 3). This result was not surprising because CDEA is not structurally related to the other allergens tested.¹³ The simultaneous reactions that occur are most likely due to coreactivity and not true cross-reactivity.

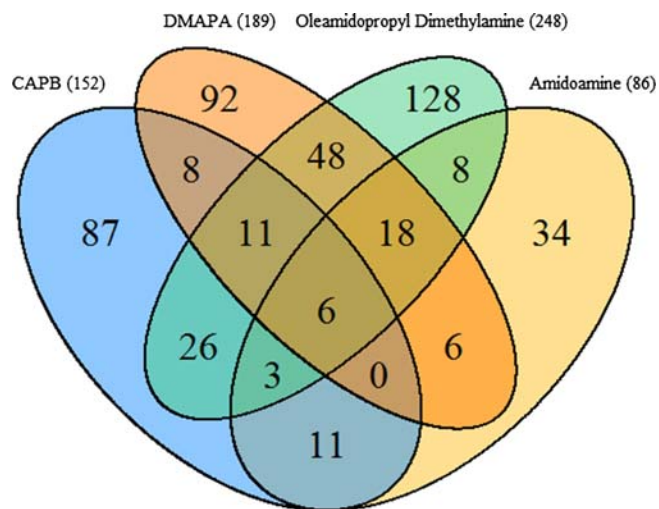
The AA was the most likely to coreact with another surfactant with only 37% (32/86) of positive reactions to AA being unique. The frequency of the other surfactants which reacted in isolation were: CAPB, 55% (84/152); DMAPA, 48% (91/189); and OPD, 51% (126/248) (Table 3). There was a significant overlap in allergic reactions between CAPB, AA, DMAPA, and OPD (Fig. 2).

Patients who tested positive to CAPB were much more likely to react to the other surfactants with the following multipliers than those who tested negative to CAPB: AA, 24.4 times; DMAPA, 12.7 times; OPD, 22.6 times; and CDEA, 7 times (Table 4). A previous study showed patients allergic to CAPB were significantly more likely to react to AA and CDEA than patients not allergic to CAPB.¹⁵

TABLE 3. Unique and Concomitant Positive Reactions for the 5 Surfactants*

	CAPB, n = 152		AA, n = 86		DMAPA, n = 189		OPD, n = 248		CDEA, n = 92	
	Number	%	Number	%	Number	%	Number	%	Number	%
CAPB	84	55	20	23	25	13	46	19	8	9
AA	20	13	32	37	30	16	35	14	4	4
DMAPA	25	16	30	35	91	48	83	34	4	4
OPD	46	30	35	41	83	44	126	51	6	7
CDEA	8	5	4	5	4	2	6	2	78	85

*Positive reactions are reported to each surfactant alone and then to each pair of surfactants. The sum of the columns is greater than 100% because some patients reacted to more than 2 surfactants.

**Figure 2.** Venn-diagram representing the cosensitivity of CAPB, AA, DMAPA, and OPD.

Our data show that there is a high degree of overlap in positive patch test reactions among 4 of the surfactants tested: CAPB, AA, DMAPA, and OPD. The DMAPA is a starting material for synthesis of CAPB and OPD.^{3,7} Both AA and DMAPA are known impurities in CAPB preparations,^{5,6} which may explain this overlap. As a result, it is difficult to use only 1 or 2 to screen for detection of allergy to the CAPB family of surfactants. Our data suggest that all 4 should be tested for optimal identification of ACD from them. Our data also show that if patients are allergic to CAPB, DMAPA, OPD, or AA then the surfactant to which they are least likely to coreact is CDEA.

TABLE 4. Odds Ratio of Reactivity to the 5 Surfactants Tested in Patients Testing Positive or Negative to CAPB

	CAPB+		CAPB–		Odds Ratio
	Number	%	Number	%	
AA	20/152	13	66/10 725	1	24.4
DMAPA	25/152	16	164/10 725	2	12.7
OD	46/152	30	202/10 725	2	22.6
CDEA	8/152	5	84/10 725	1	7

REFERENCES

1. Rietschel RL, Fowler JF. *Fisher's Contact Dermatitis*. 6th ed. Hamilton, Ontario: BC Decker Inc; 2008.
2. Corazza M, Lauriola MM, Zappaterra M, et al. Surfactants, skin cleansing protagonists. *J Eur Acad Dermatol Venereol* 2010;24:1–6.
3. Moreau L, Sasseville D. Allergic contact dermatitis from cocamidopropyl betaine, cocamidamine, 3-(dimethylamino)propylamine, and oleamidopropyl dimethylamine: co-reactions or cross-reactions? *Dermatitis* 2004;15:146–149.
4. Fiume MM, Heldreth B, Bergfeld WF, et al. Safety assessment of diethanolamides as used in cosmetics. *Int J Toxicol* 2013;32:36S–58S.
5. Schnuch A, Lessmann H, Geier J, et al. Is cocamidopropyl betaine a contact allergen? Analysis of network data and short review of the literature. *Contact Dermatitis* 2011;64:203–211.
6. Foti C, Bonamonte D, Mascolo G, et al. The role of 3-dimethylaminopropylamine and amidoamine in contact allergy to cocamidopropyl betaine. *Contact Dermatitis* 2003;48:194–198.
7. Bergfeld WF, Belsito DV, Hill RA, et al. Safety assessment of fatty acid amidopropyl dimethylamines as used in cosmetics. *Cosmetic ingredient review*. Available from: URL: <http://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR616.pdf>. Accessed July 5, 2015.
8. Suuronen K, Pesonen M, Aalto-Korte K. Occupational contact allergy to cocamidopropyl betaine and its impurities. *Contact Dermatitis* 2012;66: 286–292.
9. Fowler JF, Fowler LM, Hunter JE. Allergy to cocamidopropyl betaine may be due to amidoamine: a patch test and product use test study. *Contact Dermatitis* 1997;37:276–281.
10. McFadden JB, Ross JS, White IR, et al. Clinical allergy to cocamidopropyl betaine: reactivity to cocamidopropylamine and lack of reactivity to 3-dimethylaminopropylamine. *Contact Dermatitis* 2001;45:72–74.
11. Amin KA, Belsito DV. The aetiology of eyelid dermatitis: a 10-year retrospective analysis. *Contact Dermatitis* 2006;55:280–285.
12. Pinola A, Estlander T, Jolanki R, et al. Occupational allergic contact dermatitis due to coconut diethanolamide (cocamide DEA). *Contact Dermatitis* 1993;29:262–265.
13. Aalto-Korte K, Pesonen M, Kuuliala O, et al. Occupational allergic contact dermatitis caused by coconut fatty acids diethanolamide. *Contact Dermatitis* 2014;70:169–174.
14. Warshaw EM, Maibach HI, Taylor JS, et al. North American contact dermatitis group patch test results: 2011–2012. *Dermatitis* 2015;26: 49–59.
15. Shaughnessy CN, Malajian D, Belsito DV. Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis: reactivity to surfactants. *J Am Acad Dermatol* 2014;70:704–78.