

Allergenicity and Cross-Reactivity of Coconut Oil Derivatives: A Double-Blind Randomized Controlled Pilot Study

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Background: Counseling of patients with cocamidopropyl betaine (CAPB) allergy is difficult because the cross-reactivity of CAPB with other coconut-derived surfactants, coconut oil, and coconut fatty acids is largely unknown.

Objective: To provide pilot data regarding the cross-reactivity and allergenicity of surfactants derived from coconut oil.

Methods: A randomized double-blind controlled pilot study of 10 control patients and 12 patients previously found to be allergic to CAPB. Eleven coconut-derived surfactants, as well as coconut oil and lauric acid, were applied in random order according to standardized patch-test procedures with readings at 48 and 92 hours. The primary outcome measure was the frequency of positive patch-test reactions to each allergen.

Results: Only 3 of the 12 patients with previous reactions to CAPB reacted on retesting, and all of these reactions were doubtful. Fifty-nine percent of the study patients had reactions to triethanolamine polyethylene glycol-3 (TEA-PEG-3) cocamide sulfate as compared to none of the controls ($p = .005$).

Conclusions: Reactions to CAPB were only 25% reproducible. These results substantiate previous experience that doubtful and mild reactions to CAPB may represent irritant reactions as opposed to true allergic reactions. TEA-PEG-3 cocamide sulfate was the only agent that had a statistically significant higher rate of reactions in the study group as compared to the control group.

COCAMIDOPROPYL BETAINE (CAPB) is a zwitterionic compound commonly used as a surfactant in cosmetic and cleansing products. The first case report of allergic contact dermatitis from CAPB appeared in 1984¹; since then, many more have been reported.^{2–8} CAPB is synthesized by reacting coconut oil or coconut acid with dimethylaminopropylamine (DMAPA) to produce amidoamine, which is then further reacted with sodium monochloroacetate to form CAPB and sodium chloride⁹ (Fig 1). Depending on the grade of CAPB, various amounts of reactants and intermediates (including DMAPA, amidoamine, monochloroacetic acid, sodium chloride, and coconut fatty acids) can remain as impurities.

There has been controversy as to the allergenic component of CAPB. Foti and colleagues in Italy evaluated 10 pa-

tients who had contact allergy to CAPB and found that reactivity varied with different sources of CAPB. They also tested the patients with DMAPA (1% aqueous [aq]) and pure amidoamine (0.5% aq and 0.25% aq) and found that all 10 patients reacted; they thus concluded that allergy to CAPB is due to both amidoamine and DMAPA.¹⁰

Counseling patients with CAPB allergy is difficult because the cross-reactivity of CAPB with other coconut-derived surfactants, coconut oil, and coconut fatty acids is largely unknown. The primary objective of this double-blind randomized controlled study was to obtain pilot data on cross-reactivity among 11 structurally similar coconut-derived surfactants (CAPB, cocamide diethanolamine [DEA], cocamide monoethanolamine [MEA], cocamide monoisopropanolamine [MIPA], amidoamine, cocamidopropyl dimethylamine propionate, cocobetaine, cocamidopropyl hydroxysultaine, cocamidopropyl PG-dimonium chloride phosphate, cocamidopropylamine oxide, cocamine oxide, and TEA-PEG-3 cocamide sulfate), coconut oil, and lauric acid (a coconut fatty acid).

Methods

This double-blind randomized controlled pilot evaluation of the allergenicity of coconut oil, coconut fatty acid, and

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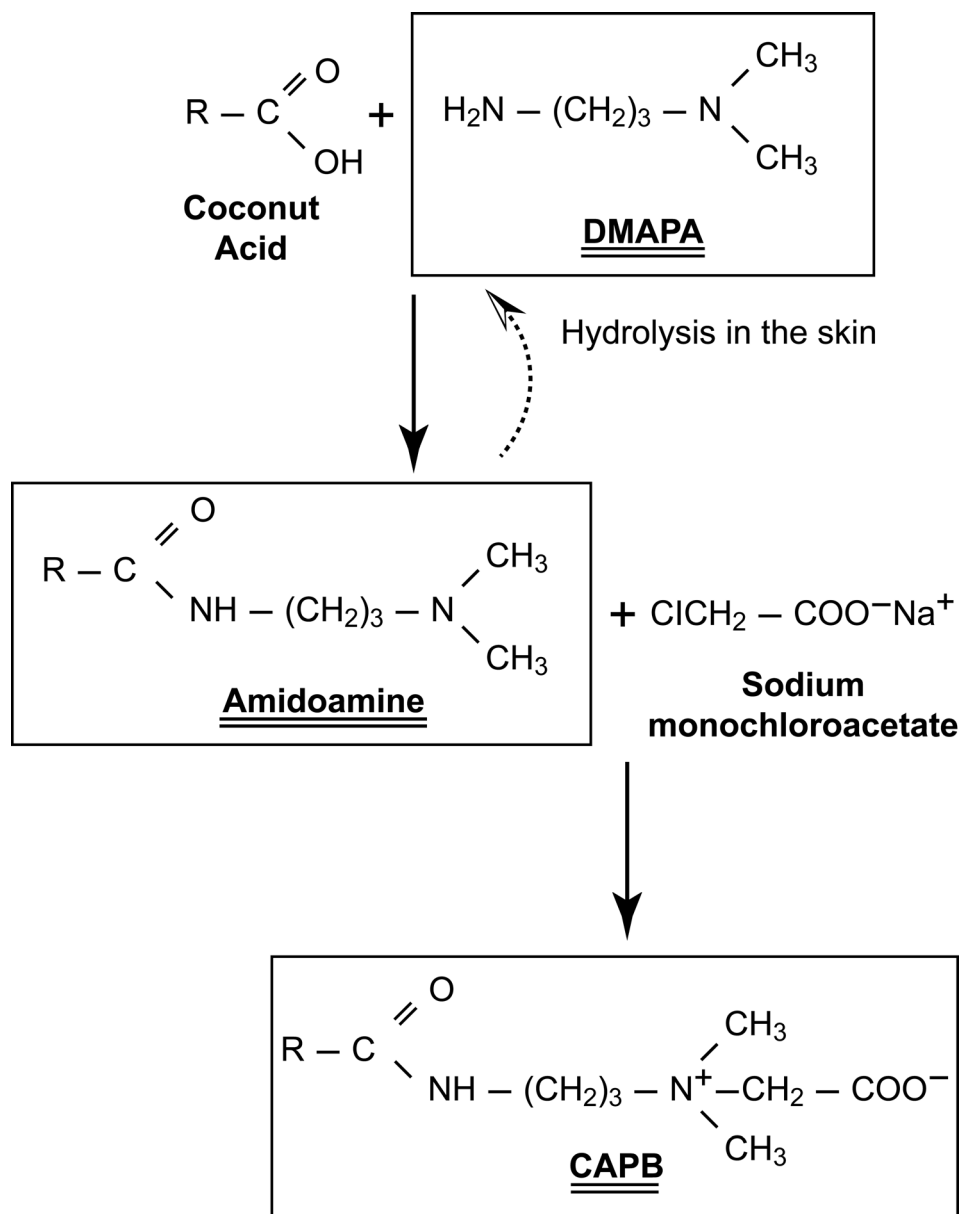


Figure 1. Synthesis of cocamidopropyl betaine (CAPB). (DMAPA = dimethylaminopropylamine) (Adapted from Vilaplana J et al.⁹; Foti C et al.¹⁰).

coconut-derived surfactants in 12 individuals who had previous patch-test positive reactions to CAPB and with 10 control patients was approved by the Human Studies Subcommittee of the Minneapolis Veterans Affairs Medical Center (VAMC) and the Institutional Review Board at the University of Minnesota. This study was conducted during fall of 2002.

Those who met the inclusion criteria included patients who had been patch-tested in the previous 3 years at the Minneapolis VAMC and University of Minnesota dermatology clinics and who had had either a doubtful or posi-

tive reaction to CAPB 1% aq (from Chemotechnique Diagnostics, Malmö, Sweden). Exclusion criteria included pregnancy or lactation, use of oral corticosteroids within 1 week of patch testing, use of intramuscular corticosteroids within 1 month of patch testing, and use of topical corticosteroids and/or topical immunomodulating agents on the back within 3 days of testing.

Of 151 patients patch-tested with CAPB at the Minneapolis VAMC and whose charts were available for review, 18 had doubtful or positive reactions. Of 124 patients patch-tested with CAPB at the University of Minnesota and whose

Table 1. Patient Demographics

	Study (n = 12)	Control (n = 10)
Gender (M:F)	5:7	0:10
Mean age in years (range)	55.3 (24–71)	52.2 (26–72)
Atopic*	6 (50%)	1 (10 %)

M = male; F = female.

*Defined as personal history of asthma, eczema, or hay fever.

charts were available for review, 14 had doubtful or positive reactions. Of these 32 patients with doubtful or positive reactions to CAPB, 12 volunteered for this study. The demographics of the study patients and the 10 controls are listed in Table 1.

CAPB 1% aq (from Chemotechnique Diagnostics), 11 coconut-derived surfactants, coconut oil and lauric acid in sterile water, and petrolatum were freshly prepared in 8 mm aluminum Finn Chambers (Allerderm, Petaluma, CA) and applied with Scanpor tape (Norgesplaster A/S, Vennesla, Norway) to the upper back of each participant (Tables 2 and 3). The antigens, petrolatum control, and aqueous control were prepared in random order according

to a computer-generated randomized list. The patch-test data sheet listed only antigen numbers, without name identification; therefore, the patient and physician were blinded to the location of the specific antigens.

At the second research visit (48 hours after the application of the patches), the patches were removed, and their locations were marked with a fluorescent highlighter. Reactions were graded after a 30-minute waiting period as mild (erythema, infiltration, possible papules), strong (erythema, infiltration, papules, vesicles), very strong (intense erythema, infiltration, coalescing vesicles, bullous, spreading), doubtful, or negative. Patients returned at 96 hours for a delayed patch-test reading, which was graded by the same standard method as at 48 hours. After the final grading of patch-test reactions, the study blind was broken so that allergen avoidance could be discussed.

The primary outcome measure was the frequency of positive patch-test reactions to each allergen. Data were tabulated with *Excel* (Microsoft Corporation, Redmond, WA) software and analyzed with *SAS* (*Statistical Analysis System*) software (SAS Institute Inc., Cary, NC). Fisher exact tests were used to examine differences in the rates of reactions

Table 2. Patch-Test Results of Study Patients

Agent	Concentration	Study Group Patient											
		1*	2*	3	4	5*	6*	7	8*	9	10*	11	12
CABP, initial reaction		+	+	D	+	†	+	D	D	+	+	+	+
Amidoamine	0.1% aq	–	–	–	–	–	–	–	–	–	–	–	–
Cocamide DEA	0.5% pet	–	–	D	–	–	–	–	–	–	–	–	–
Cocamide MEA	0.5% aq	–	–	–	–	–	–	–	–	–	–	–	–
Cocamide MIPA	1% aq	–	–	+	–	–	–	–	–	–	–	–	D
CABP	1% aq	D	–	D	–	–	D	–	–	–	–	–	–
Cocamidopropyl dimethylamine propionate	0.1% aq	–	–	–	–	–	–	–	–	–	–	–	–
Cocamidopropyl hydroxysultaine	2% aq	–	–	+	–	–	–	–	–	–	–	–	–
Cocamidopropyl PG-dimonium chloride phosphate	1% aq	–	–	–	–	–	–	–	–	–	–	–	–
Cocamidopropylamine oxide	1% aq	+	D	–	–	D	–	–	–	–	D	–	–
Cocamine oxide	1% aq	D	D	–	–	+	–	+	–	–	+	+	D
Cocobetaine	1.5% aq	–	D	D	–	+	–	+	D	D	D	+	D
Coconut oil (refined)	100%	–	–	–	–	–	–	–	–	–	–	–	–
Lauric acid (C-12 coconut fatty acid)	5% pet	–	–	–	–	–	–	–	–	–	–	–	–
TEA-PEG-3 cocamide sulfate	10% aq	D	D	D	–	–	–	+	–	–	D	D	+
Petrolatum	100%	–	–	–	–	–	–	–	–	–	–	–	–
Sterile water	100%	–	–	–	–	–	–	–	–	–	–	–	–

aq = aqueous; CABP = cocamidopropyl betaine; D = doubtful reaction; DEA = diethanolamine; MEA = monoethanolamine; MIPA = monoisopropanolamine; pet = petrolatum; TEA-PEG-3 = triethanolamine polyethylene glycol-3; + = mild reaction.

*Atopic patient.

†Scoring of initial reaction unknown.

Table 3. Patch-Test Results of Control Patients

Agent	Concentration	Control Group Patient									
		1	2	3	4	5	6	7	8	9	10*
Amidoamine	0.1% aq	—	—	—	—	—	—	—	—	—	—
Cocamide DEA	0.5% pet	—	—	—	—	—	—	—	—	—	—
Cocamide MEA	0.5% aq	—	—	—	—	—	—	—	—	—	—
Cocamide MIPA	1% aq	—	—	—	—	—	—	—	—	—	—
CAPB	1% aq	—	—	—	—	D	—	—	—	—	—
Cocamidopropyl dimethylamine propionate	0.1% aq	—	—	—	—	—	—	—	—	—	—
Cocamidopropyl hydroxysultaine	2% aq	—	—	—	—	D	—	—	—	—	—
Cocamidopropyl PG-dimonium chloride phosphate	1% aq	—	—	—	—	—	—	—	—	—	—
Cocamidopropylamine oxide	1% aq	—	—	—	—	D	—	—	—	—	—
Cocamine oxide	1% aq	D	—	—	—	—	—	—	—	—	D
Cocobetaine	1.5% aq	—	D	D	D	+	—	—	D	D	—
Coconut oil (Refined)	100%	—	—	—	—	—	—	—	—	—	—
Lauric acid (C-12 coconut fatty acid)	5% pet	—	—	—	—	—	—	—	—	—	—
TEA-PEG-3 cocamide sulfate	10% aq	—	—	—	—	—	—	—	—	—	—
Petrolatum	100%	—	—	—	—	—	—	—	—	—	—
Sterile water	100%	—	—	—	—	—	—	—	—	—	—

aq = aqueous; CAPB = cocamidopropyl betaine; D = doubtful reaction; DEA = diethanolamine; MEA = monoethanolamine; MIPA = monoisopropanolamine; pet = petrolatum; TEA-PEG-3 = triethanolamine polyethylene glycol-3; + = mild reaction.

*Atopic patient.

between study patients and controls, as well as atopic status. A significance level of 0.05 was used in all of the analyses. Given the exploratory nature of this investigation, no multiple comparison procedures were used.

Results

Tables 2 and 3 show each patient's reactions to each agent. Tables 4 and 5 summarize these results. Except in regard to TEA-PEG-3, there were no statistically significant differences between the frequency of reactions in participants and controls for mild reactions or for mild or doubtful reactions combined.

A significantly higher proportion of patients in the study group reacted to TEA-PEG-3 cocamide sulfate, compared to none in the control group ($p = .005$).

Only three patients who had had previous reactions to CAPB reacted to CAPB on retesting, and all of these reactions were doubtful ($p = .59$). Two of these patients with doubtful reactions to CAPB had possibly relevant exposures.

Of patients with a history of atopy (from both the study group and the control group), 42.9% had four or more reactions; 20% of patients with no history of atopy (from both the study group and the control group) had four or more reactions ($p = .33$).

Discussion

In our series of 12 patients, reactions to CAPB were only 25% reproducible. Two of the three patients who had repeat positive reactions to CAPB had initial mild reactions whereas the third patient had an initial doubtful reaction. Of the 9 patients who did not react to CAPB, 7 had initial mild reactions and 2 had initial doubtful reactions to CAPB.

Table 4. Summary of Reactions in Study Patients

Agent	No. of Reactions (%)	
	D	+
Cocamide DEA	1 (8)	0
Cocamide MIPA	1 (8)	1 (8)
Cocamidopropyl betaine	3 (25)	0
Cocamidopropyl hydroxysultaine	0	1 (8)
Cocamidopropylamine oxide	3 (25)	1 (8)
Cocamine oxide	3 (25)	4 (33)
Cocobetaine	6 (50)	3 (25)
TEA-PEG-3 cocamide sulfate	5 (42)	2 (17)

D = doubtful reaction; DEA = diethanolamine; MIPA = monoisopropanolamine; TEA-PEG = triethanolamine polyethylene glycol-3; + = mild reaction.

Table 5. Summary of Reactions in Control Patients

Agent	No. of Reactions (%)	
	D	+
Cocamidopropyl betaine	1 (10)	0
Cocamidopropyl hydroxysultaine	1 (10)	0
Cocamidopropylamine oxide	1 (10)	0
Cocamine oxide	2 (20)	0
Cocobetaine	5 (50)	1 (10)

D = doubtful reaction; + = mild reaction.

We pose two hypotheses regarding the lack of reproducibility of CAPB reactions in this study. The first is that the initial reactions were false positives due to irritation. Past studies have found that the general reproducibility of positive patch-test results ranges from 56 to 93% and that strong and very strong reactions are more reproducible.¹¹ An increased number of nonreproducible false-positive reactions may occur during initial patch testing owing to excited skin syndrome¹² or a history of atopy. These data suggest that doubtful and mild reactions to CAPB may be irritant reactions rather than true allergic reactions. Therefore, the relevance of doubtful and mild reactions must be carefully assessed.

The second hypothesis is that the initial reactions were due to impurities (such as DMAPA and amidoamine)^{10,13} that could have been present in the initial patches but not in the study patches. However, according to a company representative from Chemotechnique Diagnostics, their source of CAPB remained constant between 1995 and 2003. Because CAPB from Chemotechnique was used during our study as well as for the initial patch tests, we believe that the initial reactions were most likely due to irritation.

Amidoamine is a reaction product formed in the synthesis of CAPB and may play an important role in CAPB allergy. In this study, no patients reacted to amidoamine 0.1% aq. This result was unexpected because it has been documented that amidoamine may cause reactions in patients who have had previous CAPB reactions, owing to the amidoamine itself, the presence of DMAPA impurities, or hydrolysis of amidoamine to DMAPA in the skin.^{10,14} One reason for the absence of reactions in our study could be a low concentration of amidoamine (0.1% aq). Foti and colleagues showed that of 10 patients with previous reactions to CAPB, all 10 reacted to purified amidoamine at concentrations of 0.5% and 0.25% aq, but only 4 patients reacted to a 0.1% aq concentration.¹⁰

Cocamide DEA and cocamide MEA are alkanolamide nonionic surfactants and corrosion inhibitors^{15–19} that are

produced from the condensation of coconut oil with diethanolamine or monoethanolamine, respectively.¹⁵ There have been a few patients who had positive patch-test reactions to both CAPB and cocamide DEA, and there has been one report of a patient allergic to both cocamide MEA and CAPB.³ In this study, only one patient reacted to cocamide DEA, and it was a doubtful reaction. None of the patients in the control group reacted to this compound ($p = 1.00$). This lack of cross-reaction is not surprising as the molecular structure of cocamide DEA differs from that of CAPB.^{20,21} None of the study or control patients reacted to cocamide MEA.

Cocamide MIPA and cocamidopropyl PG-dimonium chloride phosphate are two additional cocamide derivatives that function as surfactants. In this study, two patients in the study group reacted to cocamide MIPA whereas none in the control group reacted ($p = .48$). None of the study or control patients reacted to cocamidopropyl PG-dimonium chloride phosphate.

Cocamidopropyl hydroxysultaine is a zwitterionic amphoteric surfactant (structurally related to CAPB but with a sulfonate group replacing the carboxylate group)^{22,23} that has been reported to cause contact allergy.²³ In this study, one patient in the study group had a mild reaction to cocamidopropyl hydroxysultaine, and one patient in the control group had a doubtful reaction to it.

Cocamidopropylamine oxide and cocamine oxide are nonionic surfactants used as emulsifiers, viscosity enhancers, foam stabilizers, emollients, lubricants, and anti-static agents.²⁴ In this study, there were four reactions to cocamidopropylamine oxide in the study group and one in the control group ($p = .32$). In the study group, all four reactions to cocamidopropylamine oxide occurred in atopic patients. In the control group, only one patient had a reaction to cocamidopropylamine oxide; this patient had no history of atopy. Cocamidopropyl oxide may contain impurities of DMAPA that could induce allergy.²⁵ In this study, 58% of patients in the study group and 20% of patients in the control group had doubtful or mild reactions to cocamine oxide ($p = .099$). The high prevalence of reactions in the control group suggests that cocamine oxide may act as an irritant at the 1% aq concentration. Further dose-ranging studies with both of these agents are needed to better define the most appropriate patch-test concentrations.

Cocobetaine is an amphoteric surfactant structurally related to CAPB, differing only by the absence of an amide group. There have been two reported cases of allergic contact dermatitis from cocobetaine.²⁶ One of the two patients also reacted to CAPB, which suggests that there may be cross-reactivity between the two surfactants.²⁶ In this

study, 75% of patients in the study group and 60% of the patients in the control group had doubtful or mild reactions to cocobetaine ($p = .65$). One of the six patients with a doubtful reaction to cocobetaine had a possibly relevant exposure. The high prevalence of reactions in the control group suggests that these reactions are irritant in nature and not truly allergic. De Groot suggests 1% aq or 2% aq concentrations of cocobetaine for patch testing. Our data suggest that a lesser concentration or a different vehicle may be required in order to avoid irritant reactions.

Residual coconut oil and impurities in coconut oil (such as fatty acids) may be present in surfactants derived from coconut oil. Lauric acid, a 12-carbon coconut fatty acid and a common constituent of bar soap, is one of the more prevalent fatty acid impurities found in CAPB. These impurities could contribute to allergic contact dermatitis.¹⁵ In this study, there were no reactions to refined coconut oil or to lauric acid.

TEA-PEG-3 cocamide sulfate is an amphoteric coconut oil-derived surfactant. Andersen and colleagues reported two patients with scalp dermatitis who reacted to both TEA-PEG-3 cocamide sulfate and CAPB.¹ In this study, a statistically significant higher number of patients in the study group reacted to TEA-PEG-3 cocamide sulfate ($p = .005$). If we assume that our 12 study patients actually had CAPB allergy, these results suggest the possibility of cross-reactivity of TEA-PEG 3 cocamide sulfate and the antigen causing the initial reaction (be it amidoamine, DMAPA, or CAPB). However, given that 5 of the 7 reactions to TEA-PEG 3 cocamide sulfate were doubtful, it is also possible that this agent was irritant at this concentration.

There are several major limitations of this study, including small sample size, low participation rate (12 of 32), lack of blinding to study or control status, likelihood of initial doubtful reactions being irritant reactions, and omission of the allergen DMAPA. We hope that the results of this pilot study will serve as the foundation for future and larger studies evaluating the potential role of DMAPA, amidoamine, and TEA-PEG-3-cocamide sulfate in CAPB allergy.

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