

Provocative use tests in CAPB-allergic subjects with CAPB-containing product

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Cocamidopropyl betaine (CAPB) has been identified as a cause of contact allergy in personal care products. Furthermore, it has been suggested that chemicals responsible are impurities, especially dimethylaminopropylamine (DMAPA). However, skin contact concentrations with these impurities, especially DMAPA, are very low. The aim of the study was to analyse whether subjects with previous positive patch tests to CAPB would react in provocative use tests of a product containing CAPB. 10 individuals with a clinical history of contact allergy to CAPB (by positive patch test and history) took part in a ROAT which used a CAPB-based shower gel at 25% (DMAPA concentration <1 ppm). None of the subjects showed positive allergic reactions. 1 of the test subjects did experience a flare of atopic dermatitis at the treatment site. Later, all 10 subjects were patch tested to 3 different concentrations of CAPB and DMAPA (0.1%, 0.3%, 1%) to verify the threshold that was capable of inducing a positive test reaction. 5/10 showed clear + reactions to 1% CAPB (typically at D3), whilst a further 3 gave marginal and/or irritant reactions. Only 1 of the subjects showed an allergic reaction to DMAPA. Finally, in uncontrolled use testing with the shower gel, none of the test subjects reported any adverse skin reactions. Thus, the study confirmed that CAPB-sensitive individuals can use a CAPB-based rinse-off product without the risk of experiencing an allergic reaction to CAPB.

Key words: allergic contact dermatitis; cocamidopropyl betaine; cosmetics; repeated open application test; shower gel; rins-off products; use tests; dimethylaminopropylamine; amidoamine.
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Since the early 1980s, there have been a number of reports which indicate that cocamidopropyl betaine (CAPB) can act as a contact allergen (reviewed in (1)). Particular products implicated as causes of the allergy have included contact lens solution, eye make up remover and shampoos. However, it has been clear that CAPB patch tests present difficulties of interpretation, as the material appears to be only a weak allergen and also may be irritating under patch test conditions (2, 3). Recently, several publications have suggested that impurities rather than CAPB itself are responsible for the allergy. Both the amidoamine intermediate (4, 5) and the starting material in CAPB production, dimethylaminopropylamine (DMAPA) (6–8), have been implicated. The evidence in the latter case may be more compelling, but has still been questioned (5, 9).

Whatever the difficulty associated with CAPB

patch tests and the issue of impurities, it is still important to know whether individuals who are allergic to this material can use commonly available personal care products which contain it without the risk of experiencing an allergic reaction. In this study, individuals with a history of allergic contact dermatitis related to CAPB sensitization participated in a repeated open application test (ROAT) (10) with a shower gel based on this surfactant. Those who did not react then proceeded to uncontrolled use of the product.

Materials and Methods

Recruitment of subjects and controls

All the volunteers in this study were informed both verbally and in writing of the nature of the work and gave their written consent to participate. Subjects with delayed contact hypersensitivity to

CAPB were recruited as follows. During 1994/5, 1063 eczema patients were tested with the standard allergen series plus cocamidopropyl betaine 1% aq. (Hermal, Reinbek, Germany). Finn Chambers on Scanpor tape (Epitest, Oy) were applied for 2 days (D). Readings were performed 20 min after removal (D2) and again at D3 and D4. Grading of reactions was according to the ICDRG scale. Complementary data included the indication for patch testing, history of atopic dermatitis, final clinical diagnosis, and localisation of eczema. 13 patients (1.2%) showed a positive allergic test reaction at D3; 3 others had a faint erythema at D2 which was no longer detectable at D3 and was presumed to be irritant. Of the 13 patients, in only 4 cases could the relevance of the positive patch test to CAPB be established (# 1–4, see Table 1), and these were selected for the present study.

The other 6 patients were referred to the department between October 1997 and April 1998, because of eczematous eruptions occurring on the scalp and/or with hand dermatitis, and showed a positive patch test reaction to CAPB 1% aq. (Hermal patch test, DMAPA content: 0.02 ppm). 3 of them (#5, 6, 9) had a personal history of atopic dermatitis. At the time of patch testing they showed no acute eczematous reactions.

20 matched adult volunteers (10 for the pre-study, 10 for ROAT and patch test), without eczema or known contact allergy, entered the study as controls, having given their informed consent.

Pre-test work

The assessment of skin reactions in the ROAT relies heavily on clinical judgement. Skin irritation can occur and the clinician has to assess carefully whether reactions are due to irritation rather than to allergic sensitization. The treatment conditions should not provoke skin irritation in non-sensitized subjects. In order to select appropriate test conditions, a pre-test with 10 control subjects (non-sensitized, 5 male, 5 female) was conducted.

Phase 1: ROAT in sensitized subjects and controls

Application of test samples was carried out by the panellist at home. The test sample was Dove shower gel (Dove Creme Dusche Extra sensitiv). The cocamidopropyl betaine raw material used for Dove (Tego-Betaine CKKB5) is controlled, with the level of the DMAPA impurity in the final product below 1 ppm, typically below 0.5 ppm.

Both the CAPB-sensitized and the control group applied the test sample (25% dilution of shower gel) to a marked test area (5×5 cm²) of the proximal part of the volar forearm 2× per day for 7

days. The panellists were instructed to apply 0.1 ml of the test sample by using a syringe (provided) and to distribute it gently by means of the finger tips (wearing vinyl gloves, provided) for about 10 s. The test samples remained on the test area for 60 s in total, after which the material was rinsed off with water. Test sites took into account hand dominance.

Test areas were assessed prior to and after the set test period by a dermatologist. Additional expert assessments during the course of the study were only intended in cases where panellists perceived adverse skin reactions before completing the study. Appropriate instructions were given to the test panel so that, during the course of the study, treatment sites could be self-assessed by panellists prior to and 10 min after each treatment. Panellists entered their assessments into a standardized report sheet (provided). Final expert assessments took place at D7 (last application) and D9, D10 and D11 to allow detection of late responders.

Phase 2: Patch testing in sensitized subjects and controls

In order better to differentiate irritant from allergic reactions and also in order to reconfirm panellists' sensitivity towards CAPB and DMAPA, all panellists were patch tested with 0.1%, 0.3% and 1.0% dilutions of CKKB (Tego-Betaine CKKB5, Goldschmidt AG, Essen, Germany, DMAPA content: 1.1ppm) and DMAPA (Goldschmidt AG, Essen, Germany), respectively. Readings took place at D2, D3 and D4 after application, using the following system:

NT	not tested
–	negative
?+	doubtful (minimal/marginal) reaction
+	weak (non-vesicular) reaction
++	strong (oedematous or vesicular) reaction
+++	extreme reaction
IR	irritant reaction

Phase 3: Product use test

All the subjects (9 of 10, all but case 5), who did not show any effect in the ROATs were asked to use Dove (CAPB-containing product) as use-test for another 4 weeks. The panellists had not used any hand soap, body wash products or shampoos that contained CAPB for the last weeks or month, since they had been told not to do so because of their sensitization. Most of them were therefore using bars of Kernseife (hard soap, free of CAPB). 9 of the initial 10 subjects participated in the product use-study. After the negative ROAT test, regardless of whether they had shown positive reac-

tions in the patch test, they were asked to use Dove creme shower gel for at least 4 weeks (not case 5). Follow-up examinations were performed in 7 subjects 4 weeks after the testing. 2 of the subjects were not available for return visits and telephone follow-up was completed.

Results

ROAT

In a pre-study with 10 controls, no skin irritation was seen with the 2× daily treatment with a 25% dilution of the CAPB-based product. Consequently, the main study with 10 CAPB-sensitized subjects was carried out. In no case were any skin reactions of an irritant or an allergic nature seen. One subject (no. 5) experienced a flare of his atopic dermatitis at the treatment site and was removed from further involvement in the study. Subject 10 reported an immediate "weal-like reaction" on D3 and D6 that disappeared within a few minutes. In this subject, the ROAT was repeated for a further week, with no effect, nor could the immediate effect be reproduced.

Patch test

After the ROAT, both the sensitized subjects and a matched control group were patch tested with dilutions of CAPB and DMAPA. The results are given in Table 1. Except for a + reaction to 1% CAPB, there was no reaction to patch tests in the control group. The absence of either present or a history of eczema together with tolerance of CAPB-containing products by this subject led to the conclusion that the reaction was irritant in nature.

With the CAPB-sensitized group, there was a little more reactivity. 5/10 showed clear + reactions to 1% CAPB (typically at D3), whilst a further 3 gave marginal and/or irritant reactions. 1 subject reacted to DMAPA with a + at all concentrations,

but failed to give a clear reaction to CAPB. A 2nd individual, who was positive to CAPB, had a doubtful reaction to DMAPA at 1%. 8 subjects failed to react to DMAPA at any concentration.

Use test

None of the 9 CAPB-sensitized subjects who participated showed a reaction during the 4-week uncontrolled use test.

Discussion

It has been recognized for many years that CAPB is an occasional contact allergen (1, 11–17). Specific cases of allergic contact dermatitis from CAPB have often been associated with a particular product/use of this material, including contact lens cleaners, eye make-up remover and shampoo (13, 18–20). The last-mentioned use has been implicated as a contributory factor in hand dermatitis experienced by hairdressers (15, 21). It has also been apparent however that clinical evaluation of patients has been complicated by the irritancy of CAPB used in testing (2, 3). Such an assessment is also indicated by the results contained in the present work.

What could be the cause of CAPB allergy? Based on our understanding of the chemistry of allergic contact dermatitis (reviewed in 22), CAPB itself is very unlikely to be a skin sensitizer (23). Consequently, it is most probable that an impurity of some kind (a contaminant, a by-product or a residue) is responsible. This concept was the basis of work on the amidoamine intermediate in CAPB production (3). However, whilst this showed that some CAPB-positive individuals did react to the amidoamine intermediate, other CAPB patch test positive patients did not. Thus its rôle as an important sensitizing impurity in CAPB was unproven. Another potential impurity in CAPB is the starting diamine, DMAPA. This was already

Table 1. Results of patch testing with CAPB and DMAPA

Subject no.	CAPB			DMAPA		
	1.0%	0.3%	0.1%	1.0%	0.3%	0.1%
1	?+/?+/- ^{a)}	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
2	+/+/+	-/?+/?+	-/-/-	-/-/-	-/-/-	-/-/-
3	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
4	IR/IR/IR	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
5	-/+/?+	-/-/-	-/-/-	-/?+/-	-/-/-	-/-/-
6	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
7	-/+/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
8	?+/+/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
9	-/+/?+	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
10	?+/IR/IR	-/-/-	-/-/-	-/+/+	-/+/+	-/+/+

^{a)}Results given as D2/D3/D4 data; scoring as in Materials and Methods section.

known to be a human contact allergen, including during the manufacture of CAPB (24). Subsequently, Angelini et al (6, 7, 25) undertook various studies which strongly implicated DMAPA as the probable cause of CAPB allergy. Most recently, attention has been drawn again to the amidoamine by the studies of Fowler et al (5), whose CAPB-positive patients failed to react to DMAPA, but who did show a propensity to respond to the amidoamine (5).

In a practical sense, knowledge of the sensitizing impurities in CAPB would allow the manufacturing processes to be adjusted to limit their concentration and so minimize or even eliminate the risk of allergic reactions in skin. Since our information is imperfect, CAPB has to be sourced with both DMAPA and amidoamine minimized (<10 ppm and <0.1%, respectively). To confirm that these levels were safe in personal wash-type products even for subjects with a confirmed history of CAPB allergy, we carried out a ROAT study. With the shower gel type of product used, 2× daily skin contact with a 25% concentration for a total of 2 min represents a reasonable degree of exposure. The results show clearly that under these conditions no allergic response was elicited. The data from the control group as well as the test group confirmed that there was no skin irritation induced under these test conditions. Further uncontrolled use testing with the product in the CAPB-sensitive panel did not give rise to any indication of an allergic eczema. This data contrasts with that from Fowler, who showed that use tests in CAPB-allergic subjects were often positive (26).

Patch testing of the CAPB-allergic subjects produced interesting results (Table 1). The observed reactions showed a typically crescendo pattern (with no reactions at D2 but reactions occurring by D3) suggesting a true allergic reaction. But in only 1/2 half could the previous positive patch test be reproduced. Given that we had carefully selected the individuals on the basis not only of a past positive patch test, but also a clearly associated history of intolerance to CAPB-containing products, this outcome was rather surprising. It may be due to a change in the CAPB patch test material – at least in terms of impurities. This itself then opens up interesting questions for the future detection of CAPB allergy. Clearly, if the quality of CAPB is improving generally, then allergy to this material may become a thing of the past. There is already some indication that this may in fact be the case (27).

In conclusion, we have shown that, at least where the source of CAPB is of sufficiently high quality, then individuals with allergy to CAPB may

use safely personal wash products based on this amphoteric active.

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