

Is the irritant benzalkonium chloride a contact allergen? A contribution to the ongoing debate from a clinical perspective

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Background: Benzalkonium chloride (BAC) is a well-recognized irritant. However, doubts exist that it is also a contact allergen.

Objective: Analysis of clinical patch test data addressing the reaction profile and synchronous reproducibility of BAC 0.1% in petrolatum (pet.) and possible increases in risk of BAC contact allergy in certain (occupationally exposed) subgroups.

Patients / Methods: Data of 42 898 patients tested with BAC 0.1% in pet. in 3 different series (topical drugs, ophthalmics, and disinfectants) in the departments of the Information Network of Departments of Dermatology (<http://www.ivdk.org>) between 1996 and 2006 was analysed.

Results: Overall, morphologically 'positive' reactions were rare, 0.6–1.5%, with a total of 41 stronger positive reactions. Concordance, assessed in 3322 patients tested in duplicate, was low (kappa coefficient 0.15, 95% CI: 0–0.31). Positive test reactions were observed significantly more often in the disinfectants series compared with the 2 other series, indicating that suspected exposure to disinfectants may be associated with sensitization. However, variation of stronger BAC test positivity across potentially relevant (occupational) groups was non-significant.

Conclusion: This analysis of routine clinical data and a number of previous reports add further, if weak, evidence to the notion that BAC is a contact allergen, albeit a very rare one.

Key words: benzalkonium chloride; CAS 8001-54-5; clinical epidemiology; contact allergy; patch test. © Blackwell Munksgaard, 2008.

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Recently, the skin toxicity of the quaternary ammonium compound benzalkonium chloride (BAC) has been reviewed, and BAC classified as an irritant but not an allergen (1). However, while the irritant properties of BAC are not disputed, some doubt remains whether BAC is also a contact allergen, albeit a weak one (2–6). The aim of the present analysis of data from the Information Network of Departments of Dermatology (IVDK) contact allergy surveillance network is to try to provide new data, striving for a more confident classification of BAC.

Patients and Methods

The IVDK (<http://www.ivdk.org>) now comprises more than 45 departments of dermatology in Germany, Austria, and Switzerland. The patch test procedure follows international standards (7) further refined by the German Contact Dermatitis Research Group (DKG) (8). Standardized patch test data along with basic demographic and clinical information are regularly collected in an anonymous format and analysed (9, 10). All participants of the IVDK are members of the DKG, which issues recommendations regarding

the composition of the standard and special patch test series (current recommendations under <http://www.ivdk.gwdg.de/dkg/>). During the study period (1996–2006), BAC at a concentration of 0.1% in petrolatum (pet.) had been tested selectively in patients suspected to be exposed to preservatives or disinfectants, respectively, in 3 different test series (Table 1). In addition, BAC had been included in a number of other, department-specific test series or was tested in different concentrations and vehicles, respectively. This data will not be considered in the following analyses.

Results

In view of the disparate use of BAC 0.1% in pet. in different test series applied to different sets of patients, results will be presented both stratified for use in the test series and globally. The reaction profile of BAC is shown in Table 1. Evidently, the yield of all, except doubtful, reactions is significantly higher in the disinfection series, most strikingly regarding ++/+++ reactions, the latter observation confirmed in a multifactorial analysis adjusted for sex, age, and leg dermatitis as potential confounders. Moreover, the reaction profile in terms of reaction index (RI) (11) and positivity ratio (PR) (12) is more favourable compared with the other 2 series.

A considerable number of patients were tested in duplicate or, in 79 instances, even in triplicate with BAC 0.1% in pet. Comparing the test results of these 3322 patients, considerable discrepancies can be noted (Table 2). Collapsing the 4×4 table into a 2×2 table, aggregating negative with doubtful/irritant and weak positive reactions with (just 1) stronger positive reaction, respectively, a simple kappa coefficient of 0.15 (95% CI: 0–0.31) is found. Hence, reproducibility of + reactions was low. No conclusion is possible with

Table 2. Cross-tabulation of patch test results where benzalkonium chloride 0.1% in petrolatum was applied in duplicate ($n = 3322$ patients)

	Negative	?/IR	+	++/+++
Negative	3241	18	16	1
?/IR	24	4	1	0
+	13	1	3	0
++/+++	0	0	0	0

regard to the reproducibility of stronger reactions as only 1 case with a ++/+++ reaction was tested in duplicate (Table 2).

The clinical and demographic profile regarding potentially important items of patients reacting positively versus non-positively (+ or ++/+++) to BAC in the 3 series yielded no remarkable findings regarding the 'ophthalmics' and the 'topicals' series. Results for the 'disinfectants' series are shown in Table 3.

As dental assistants had been identified as a subgroup at relatively high risk of BAC contact sensitivity (CS) in a previous analysis (2), a separate bivariate analysis focussed on this and selected other (non-) occupational groups, trying to yield comparative evidence on a possible, exposure-associated increase of CS frequency, stratified for the 2 outcomes (+ versus ++/+++) – Table 4. Indeed, ++/+++ reactions, albeit just 2, were more common among dental assistants; however, as a result of the relative rarity of these events, this is not a significant finding.

Prior to 2001, sodium lauryl sulphate (SLS) had been tested only by few centres and possibly in selective ways. Hence, overlap with the use period of the topicals series was limited, yielding a relatively small number ($n = 1785$) of patients tested with SLS 0.25% aqueous. Among these, the proportion of positive (irritant) SLS reactions was higher in patients testing positively to BAC. This difference was also found in the more currently

Table 1. Reaction profile of benzalkonium chloride 0.1% in petrolatum used in different test series*

Reaction (parameter)	Ophthalmics [n (%)]	Disinfectants [n (%)]	Topicals [n (%)]	Total [n (%)] [†]	OR (95% CI)
Period used	1996–2006	2000–2006	1996–2001		
n (tested)	4422	8152	33 725	42 898	
IR	8 (0.18)	16 (0.19)	7 (0.02)	30 (0.07)	5.0 (2.3–10.9)
?	46 (1.04)	56 (0.71)	279 (0.83)	377 (0.88)	0.81 (0.60–1.1)
+	39 (0.88)	97 (1.19)	187 (0.55)	320 (0.75)	2.0 (1.6–2.6)
++/+++	2 (0.04)	24 (0.29)	15 (0.05)	41 (0.09)	6.7 (3.4–13.2)
% Pos (crude)	0.93	1.48	0.60	0.84	
% Pos (stand.) with 95% CI	0.80 (0.53–1.07)	1.47 (1.19–1.74)	0.59 (0.50–0.67)	0.82 (0.73–0.91)	
Positivity ratio (%)	95.1	80.2	92.6	88.7	
Reaction index	–0.137	0.247	–0.172	–0.062	

OR, odds ratio; Pos, positive; Stand., age and sex standardized.

*The crude OR along with accompanying exact 95% CI quantifies the risk of a certain reaction category (reference: negative reaction) obtained with the disinfectants series (reference: other 2 series).

[†]Maximum reaction in case of duplicate or triplicate testing.

Table 3. Relevant demographic and clinical profile of patients patch tested with BAC 0.1% in petrolatum in the disinfectants series, stratified for reactivity to BAC*

	<i>n</i> tested	<i>n</i> (%) +	<i>n</i> (%) ++/+++
MOAHLFA factors			
Male	2504	31 (1.240)	11 (0.439)
Occupational	2410	34 (1.411)	6 (0.249)
Atopic dermatitis	1444	18 (1.247)	0
Hand dermatitis	4680	33 (0.705)	5 (0.107)
Leg dermatitis	1358	32 (2.356)	12 (0.884)
Face dermatitis	765	6 (0.784)	3 (0.392)
Age 40 years and above	5442	63 (1.158)	17 (0.312)
Selected present occupation			
Old-age pensioner	1990	32 (1.608)	9 (0.452)
Housewife	511	4 (0.783)	1 (0.196)
Pupil and student	200	5 (2.500)	1 (0.500)
Dental nurse/assistant	153	3 (1.961)	2 (1.307)
Cleaner	413	7 (1.695)	1 (0.242)
Nurse	790	5 (0.633)	0
Physician and other HCW	445	2 (0.449)	1 (0.225)
Geriatric nurse	280	3 (1.071)	0
Selected suspected contactants[†]			
Topical medication	2817	44 (1.562)	14 (0.497)
Cosmetics	2371	33 (1.392)	9 (0.38)
Disinfectants	2430	34 (1.399)	6 (0.247)
Soap etc.	722	9 (1.247)	2 (0.277)
Cleaning products	638	8 (1.254)	1 (0.157)
Patch application 2 days	4527	49 (1.082)	8 (0.177)
<i>n</i> with positive reactions [‡]	4843	90 of 97	23 of 24
Among these, number of positive reactions [mean; median (IQR)]	3.1; 2 (1–4)	5.2; 4 (2–7)	11; 9 (5–17)
<i>n</i> with irritant/doubtful reactions [‡]	3528	63 of 97	15 of 24
Among these, number of irritant or doubtful reactions [mean; median (IQR)]	2.5; 2 (1–3)	2.9; 2 (1–4)	2.7; 2 (1–4)

BAC, benzalkonium chloride; HCW, health care worker; IQR, inter-quartile range.

*Row percentages given.

[†]Multiple (up to 3) responses possible.

[‡]Excluding BAC.

used 'disinfectant' series, where it was significant [42.3% (95% CI: 28.7–56.8%) versus 19.3% (95% CI: 18.1–20.6%)], and in the fewer patients tested with the 'ophthalmic' series, where it was non-

significant [55.6 (95% CI: 21.2–86.3) versus 22.0 (95% CI: 19.3–25.0)]. Restricting this comparison to patients reacting ++ or +++ to BAC as 'positive' versus the respective remainder accentuated these differences further.

Discussion

Addressing the question posed in the title, we have analysed a large set of 'routine' clinical data from the IVDK network. In this data, the degree of detail, such as results of verification tests (Repeated Open Application and Provocative Use Test) or product breakdown tests, is limited. Still, we have tried to add further evidence to the issue.

The first analysis addressed the reaction profile of BAC tested as 0.1% in pet. The low and even negative RI and the high PR indicate this test substance to be 'problematic', in accordance with previous analyses (5, 12). The concordance between results of synchronously tested BAC is very low. In comparison, 'proper' allergens exhibit much higher kappa values upon synchronous duplicate testing, such as 0.86 (95% CI: 0.83–0.90) in the case of nickel, 0.81 (95% CI: 0.75–0.87) in case of *Myroxylon pereirae* resin, or 0.56 (95% CI: 0.42–0.71) considering formaldehyde, which is an allergen with notoriously low reproducibility (13). All these allergens perform significantly better than BAC. Rather, BAC seems to be similar to phenylmercuric acetate, which is considered as being mainly an irritant when patch tested (14).

The occurrence of erythematous, infiltrated – i.e. 'morphologically positive' – test reactions at D3 has been observed also with a few clear-cut irritants (15), rendering the distinction between irritant and allergic reactions solely based on morphology and even time-course unreliable – be it for a fairly limited number of test preparations. Often, the consideration of the clinical relevance of such reactions will aid the distinction between irritant and allergic reactions (16). However, in our view, the conclusiveness of such evidence is sometimes limited by the fact that even though a definite exposure to, for example,

Table 4. Frequency and risk of different grades of 'positive' reactions to benzalkonium chloride in occupational subgroups among patients tested with the disinfectants series*; OR (95% confidence interval)

	Negative/?/IR	+	++/+++	Row sum
Pupils and students	194; 1 (reference)	5; 2.6 (0.80–6.5)	1; 2.5 (0.06–16.8)	200
Dental assistants	148; 1 (reference)	3; 2.0 (0.40–6.4)	2; 6.5 (0.70–29.4)	153
Old-age pensioners	1949; 1 (reference)	32; 1.7 (1.0–2.6)	9; 2.2 (0.82–5.7)	1990
Remaining occupations	5741; 1 (reference)	57; 1 (reference)	12; 1 (reference)	5810
Column sum	8032	97	24	

OR, odds ratio.

*Risk relative to (i) negative/?/IR reactions and (ii) to 'remaining occupations' estimated by the OR accompanied by exact 95% CI.

BAC-containing eye drops, surface disinfectants, or antiseptic bath solutions may have existed and even causation or aggravation of contact dermatitis may have been noted by the patient, this might still have been caused by irritation (not necessarily by BAC alone) and not to contact allergy.

Still, the fact that a substance is difficult to test and may cause irritant, false-positive reactions does not rule out this substance being an allergen, albeit in exceptional cases. If BAC were exclusively an irritant, no differences in the frequency of positive reactions between different subgroups of patients defined by the exposure-guided application of certain test series should occur. However, our analyses identified clear differences with regard to the stronger reactions (++/+++), normally interpreted as allergic. Taking the 3 groups defined by the patch test series applied as groups differently exposed to BAC, namely BAC as a disinfectant versus BAC as a preservative, it is interesting to note that the use concentrations of BAC are about 2 orders of magnitude higher in disinfectants (e.g. 1–20% in typical surface disinfectant concentrates) than in topical products intended for application to the skin or mucous membranes (typical concentration $\leq 0.01\%$ as preservative and 0.1% as active ingredient) (<http://www.rote-liste.de>, last accessed 25 October 2007). Therefore, it can be assumed that BAC (i) can induce specific contact sensitization, given sufficient exposure (usually by disinfectants), and (ii) can elicit unequivocal allergic patch test reactions after sensitization by a sufficient concentration.

Conclusions

From the results of the present study, 2 main conclusions regarding the significance of the irritant BAC as contact allergen can be drawn:

- (1) The majority of + reactions to BAC can probably be interpreted as false positive as (i) these reactions are hardly reproducible and (ii) their proportions in the 3 assumed exposure groups differed by a factor of just 2 (possibly because of a few cases of true sensitization). Hence, positive patch test results if only + (erythema, infiltration, and possibly papules) should be interpreted with great caution and verified with appropriate validation tests.
- (2) Those exposed to, and therefore tested with, disinfectants exhibited a significantly more than sixfold higher proportion of ++/+++ reactions. These reactions should probably be interpreted as allergic and not

as irritant for 2 reasons: (i) the morphology of the reaction (erythema, papules, and vesicles) is indicative of allergic contact dermatitis and (ii) these reactions accumulate in the 'high-exposure' group and are thus plausible.

On the basis of these two observations, it may be concluded that the irritant BAC has sensitizing properties but is a very rare contact allergen.

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