

Prevalence of benzocaine and lidocaine patch test sensitivity in Denmark: temporal trends and relevance

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Summary

Background. Allergens included in the European baseline series should result in positive patch test reactions in at least 1% of a patch test population. Inclusion of local anaesthetics other than benzocaine in the baseline series has previously been debated.

Objectives. To investigate temporal trends of benzocaine and lidocaine allergy in dermatitis patients who underwent routine patch testing in a tertiary referral patch test centre, and to clarify and discuss whether lidocaine and benzocaine should be included in routine series.

Methods. Dermatitis patients who underwent routine patch testing with benzocaine as a part of the European baseline series between 1985 and 2010 ($n = 19\,347$) and dermatitis patients who underwent routine patch testing with lidocaine between 1994 and 2001 ($n = 6265$) and between 2007 and 2009 ($n = 1360$) were included.

Results. The overall prevalences of contact allergy were 0.5% (benzocaine), 0.3% (lidocaine for the period 1994–2001), and 0.14% (lidocaine for the period 2007–2009). Current relevance was observed in 10% of those with benzocaine allergy and in 5% of those with lidocaine allergy.

Conclusions. Benzocaine and lidocaine allergy is infrequent in Danish dermatitis patients. Lidocaine should only be used for aimed testing, and benzocaine should be removed from the baseline series used in Denmark.

Key words: benzocaine; dermatitis patients; lidocaine; local anaesthetics; patch test reactivity.

Local anaesthetics (LAs) are widely used in topical preparations and for injection purposes. Pharmacologically, they may be divided into ester and amide compounds, on the basis of their intermediate chain linkage (1). Allergic contact dermatitis following exposure to benzocaine, an ester LA used in, for example, sunburn relief lotions and haemorrhoid ointments, has frequently been

reported (2–5). Hence, benzocaine has been a part of the European baseline series for decades. Lidocaine is an amide LA that is often used for injections but also in topical preparations, for example ointments for the treatment of pruritus ani (6) and lotions for sunburn relief (7). In Denmark, lidocaine and benzocaine are currently available in some topical preparations, but their use is generally restricted to prescription products. Thus, benzocaine is used in over-the-counter antitussives, and lidocaine is prescribed for the treatment of pruritus, sunburn, bites, and wounds (prior to change of wound dressings). Allergic contact dermatitis caused by lidocaine is generally less frequent than benzocaine allergy (1).

As a rule of thumb, allergens included in the European baseline series should result in positive patch test

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reactions in at least 1% of a patch test population. The possible inclusion of other LAs in the baseline series has previously been debated. Thus, Weightman and Turner suggested that lidocaine should be added to the European baseline series (8), and it has also been stressed that the inclusion of a 'caine' mix (e.g. benzocaine, dibucaine, and tetracaine) could be beneficial (9) (as used in the TRUE Test®). Furthermore, it is generally accepted that the choice of allergens used for patch testing should rely on local use and prescription habits, and that it hence may change over time as new products are introduced (10). We set out to investigate temporal trends of benzocaine and lidocaine allergy in dermatitis patients who underwent routine patch testing in a tertiary referral patch test centre between 1985 and 2010. Lidocaine was only used for routine testing during 1994–2001 and 2007–2009. The study aimed to clarify and discuss whether lidocaine and benzocaine should be included in routine patch testing series.

Materials and Methods

Study population

Dermatitis patients who underwent routine patch testing with benzocaine as a part of the European baseline series between 1 January 1985 and 30 June 2010 and dermatitis patients who underwent routine patch testing with lidocaine between 1 January 1994 and 31 December 2001 and between 21 August 2007 and 31 August 2009 were included. The MOAHLFA (Male, Occupation, Atopic dermatitis, Hand eczema, Leg dermatitis, Facial dermatitis, Age above 40 years) index was not routinely registered throughout the study period. Thus, MOAHLFA registrations date back to 1994 (but only to 2001 for 'Facial dermatitis').

Patch testing

Testing was performed throughout the study period with benzocaine 5% in petrolatum and lidocaine 15% pet., using Finn Chambers® (8 mm; Epitest Ltd, Oy, Finland) on Scanpor® tape (Norgesplaster A/S, Alpharma, Vennesla, Norway). Patch test ingredients were from Hermal (Reinbek, Germany). Patch tests were applied to the upper back and were occluded for 2 days. Readings were performed on day 2, on day 3 or day 4, and on day 7, according to the recommendation of the International Contact Dermatitis Research Group (11). Thus, homogeneous redness and infiltration in the entire test area was scored as a 1+ reaction. Homogeneous redness, infiltration and vesicles in the test area were

scored as a 2+ reaction, and homogeneous redness, infiltration and coalescing vesicles in the test area were scored as a 3+ reaction. A 1+, 2+ or 3+ reading was interpreted as a positive response. An irritant response, a doubtful reading (+?) or a negative reading was interpreted as a negative response. On the basis of the medical history, the physician judged whether benzocaine and lidocaine allergy was of current, past or unknown relevance.

Statistical analysis

The χ^2 -test was used to test for statistical differences; 95% confidence intervals (CIs) were used to assess whether the overall prevalence of benzocaine and lidocaine allergy exceeded 1%, the minimum prevalence suggested for allergens included in the baseline series. Data analyses were performed with SPSS™ (SPSS, Chicago, IL, USA) for Windows™ (release 15.0).

Results

A total of 19 347 dermatitis patients (64.6% women and 35.4% men) aged 4–99 years were patch tested with benzocaine between 1985 and 2010; 6265 patients (64.6% women and 35.4% men) were patch tested with lidocaine between 1994 and 2001; and finally, 1360 dermatitis patients (68% women and 32% men) were patch tested with lidocaine between 2007 and 2009. Their main characteristics have been reported previously (12, 13). The MOAHLFA index is shown in Table 1. The MOAHLFA index for lidocaine-allergic patients showed a higher proportion of patients older than 40 years, and with presence of leg ulcer and absence of hand eczema. A higher prevalence of facial dermatitis and leg ulcers was observed in patients with a positive patch test response to benzocaine than in all patch-tested dermatitis patients.

The overall prevalence of benzocaine allergy was 0.5% (95% CI 0.44–0.64) (men, 0.4%; women, 0.6%; $p = 0.01$), and the overall prevalence of lidocaine allergy was 0.3% (95% CI 0.17–0.40) (men, 0.3%; women, 0.3%; $p = 0.78$) (i.e. 0.3% for the period 1994–2001 and 0.14% for the period 2007–2009). No changes in the prevalence or patch test reactivity (i.e. a change in the strength of patch test reactions) to benzocaine and lidocaine were observed over the study period, except for a slight decrease in lidocaine allergy in recent years ($p_{\text{trend}} = 0.44$) (Fig. 1) (15). Among 103 patients with positive patch test reactivity to benzocaine, 10 (9.7%) and 12 (11.6%) were judged to have benzocaine allergy of current and past relevance, respectively. Among 18

Table 1. MOAHLFA index in dermatitis patients who were patch tested at Gentofte Hospital during 1994–2009 (facial dermatitis was only registered from 2001)

Frequency of variables	All patients (n = 13 208) % (n/n _{total})	Benzocaine- allergic patients (n = 66) % (n/n _{total})	Lidocaine- allergic patients* (n = 18) % (n/n _{total})
Males	34.9 (4607)	16.7 (11)	33.3 (6)
Occupational dermatitis	14.0 (1848)	7.6 (5)	0
Atopic dermatitis	13.7 (1804)	12.1 (8)	5.6 (1)
Hand dermatitis	33.1 (4378)	37.9 (25)	0
Leg ulcers	8.3 (1095)	18.2 (72)	27.8 (5)
Facial dermatitis	21.1 (1547) [†]	37.8 (14) [‡]	—
Age > 40 years	66.1 (8734)	65.2 (43)	94 (17)

The MOAHLFA (Male, Occupation, Atopic dermatitis, Hand eczema, Leg dermatitis, Facial dermatitis, Age above 40 years) index shows the characteristics of patients tested at a patch test clinic, and may be used for comparison (26).

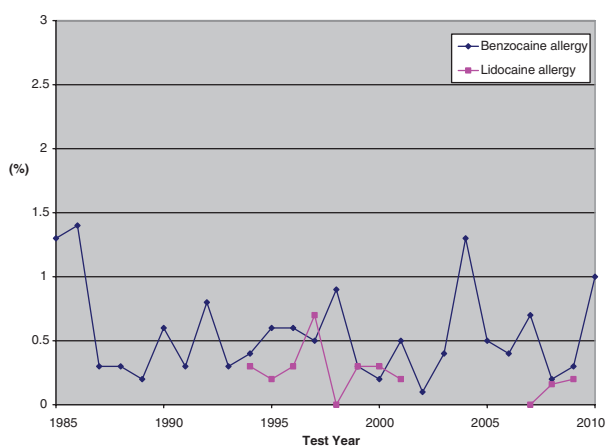
*For the period 1994–2001.

[†]7328 dermatitis patients since 2001.

[‡]37 benzocaine-allergic patients since 2001. (Facial dermatitis was only registered from 2001.)

patients with patch test reactivity to lidocaine detected between 1994 and 2001, 1 (5.5%) had contact allergy of current relevance and 1 (5.5%) had contact allergy of past relevance. Finally, among the 2 patients with lidocaine allergy diagnosed between 2007 and 2009, 1 had contact allergy of current relevance and 1 had contact allergy of unknown relevance.

Table 2 shows an overview of cross-reactivity between benzocaine allergy and contact allergy to paraben mix,

**Fig. 1.** Temporal development of benzocaine and lidocaine allergy among dermatitis patients undergoing routine patch testing at Gentofte Hospital, Denmark.**Table 2.** The prevalence of concomitant contact allergy to benzocaine and other para group chemicals in dermatitis patients tested between 1985 and 2009

Concomitant contact allergy to:	Benzocaine- allergic patients % (n/n _{total})*
<i>p</i> -phenylenediamine (PPD)	29.1 (28/96)
Paraben mix	7.8 (8/103)
<i>N</i> -isopropyl- <i>N'</i> -phenyl- <i>p</i> -phenylenediamine (IPPD)	5.8 (6/103)
PPD, paraben mix, or IPPD	33.0 (34/103)

*(n/n_{total}) = number of concomitant reactions/total number of patients with positive patch test reactivity to benzocaine.

p-phenylenediamine (PPD), and *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine (IPPD) (Table 2). About one-third had concomitant contact allergy to benzocaine and one of the three chemicals. Of these, 10 were judged to have benzocaine allergy of either current or past clinical relevance. No simultaneous patch test reactions to lidocaine and benzocaine were observed during the study period.

Discussion

This study showed that the overall prevalence of benzocaine allergy was 0.5% (95% CI 0.44–0.64) over a 26-year patch test period in Denmark, and that lidocaine allergy was infrequent, reaching, respectively, 0.3% and 0.14% for the periods 1994–2001 and 2007–2009. Figure 1 shows the temporal trends of benzocaine and lidocaine allergy. In only three instances did the prevalence of benzocaine allergy exceed 1% (1986, 2004, and 2010). The prevalence of lidocaine allergy remained low. On the basis of our observation, benzocaine and lidocaine should not be included in the European baseline series applied in Denmark (and perhaps elsewhere), but rather should be used for aimed testing. A recent study from Finland showed that 4% of 620 dermatitis patients undergoing aimed patch testing with topical medicaments including topical anaesthetics had contact allergy to an LA (16). Among 25 patients with LA contact allergy, dibucaine allergy was observed in 20, benzocaine allergy in 3, and lidocaine allergy in 2. The authors concluded that dibucaine-containing perianal medicaments were the most frequent sources of LA contact allergy. Thus, even when aimed patch testing for LA allergy was performed in a northern European centre, the prevalence of lidocaine and benzocaine allergy remained low. Sidhu et al. performed a 10-year retrospective study for the period 1988–1998, and found that benzocaine allergy was uncommon (0.4%) in the UK, and that more positive reactions were observed for dibucaine and tetracaine (17).

Another UK study, including 3000 consecutive patients who were patch tested with a mix of benzocaine, amethocaine, and cinchocaine, showed that 2.8% were allergic to this mix (9). Forty caine-allergic patients were additionally tested with the constituents of the mix, and 52.5% patients were sensitive to amethocaine and/or cinchocaine but not to benzocaine. Very recent patch test data from the European Surveillance System on Contact Allergies showed that 1–1.3% of dermatitis patients patch tested in different European clinics had benzocaine allergy, and that no regional variations could be identified (18). Taken together, these findings show that benzocaine allergy is generally infrequent in European dermatitis patients and general populations (19–22), and that benzocaine seems not to be useful for screening purposes.

The epidemiology of caine allergy is slightly different elsewhere in the world, probably as a result of variations in the availability and use of LAs in different countries. Thus, Warshaw et al. recently evaluated the prevalence and pattern of contact allergy to LAs among 10 061 patients tested within the North American Contact Dermatitis Group (NACDG) (23). The prevalence of benzocaine allergy between 1984 and 2001 was 1.7–3.5% (23). Beginning in 2001, the NACDG standard series was expanded to include tetracaine, lidocaine, dibucaine, and prilocaine. For the period 2001–2004, 3.4% of patients had at least one contact allergy to an LA. No sex difference was observed. Benzocaine was the most prevalent allergen, accounting for 50% of positive reactions (the overall prevalence was 1.7%), followed by dibucaine (28%), lidocaine (19%) (overall prevalence of 0.7%), tetracaine (11%), and prilocaine (2%). A total of 6 patients had concomitant patch test reactions to lidocaine and benzocaine. The authors concluded that, in North America, benzocaine is still a useful screening agent for contact allergy to LAs, despite the fact that it detected only 50% of contact allergy cases. An older report from Australia revealed that 0.3–0.7% of Australian dermatitis patients had lidocaine allergy (8, 23). Among 2585 dermatitis patients recently tested in Hong Kong, 1.4% had benzocaine allergy (24).

An attempt to study the epidemiology of benzocaine allergy included assessment of clinical relevance. Data analysis revealed that 10% and 11%, respectively, had benzocaine allergy of current and past relevance. Similarly, the proportions of lidocaine-allergic patients with current and past relevance were very low (each 5.5%). Our data are slightly different from relevance data from North America (23). Warshaw et al. reported that 34% and 16% of their patients,

respectively, had benzocaine allergy of current and past relevance. Regarding lidocaine allergy, the prevalences of current and past relevance were, respectively, 36% and 13% (23). Our study suggests that, in Denmark, not only was the overall prevalence of benzocaine and lidocaine allergy very low, but so was the clinical relevance.

We assessed cross-reactivity patterns with other chemicals from the para group (Table 2). Among patients with benzocaine allergy, 33% had a concomitant reaction to PPD, parabens, or IPPD. PPD was by far the most important cross-reagent, as it was observed in 29% of patients with benzocaine allergy. It is unknown whether PPD or benzocaine allergy came first, but it is possible that up to one-third of patients with benzocaine allergy have been primarily sensitized to PPD, and that benzocaine allergy is a result of cross-reactivity. In support of this view, we recently showed that only 2% of 106 patients with PPD allergy from our department had concomitant benzocaine allergy (25). However, surprisingly, among a total of 22 benzocaine-allergic patients with either past or current clinical relevance, 10 had concomitant contact allergy to PPD, IPPD, and/or parabens. Thus, cross-reactivity to other para group chemicals in patients with benzocaine allergy may be a marker of clinical relevance and strength of allergic contact dermatitis. This could be of clinical relevance for physicians who interpret patch test data. A weakness of our data includes the absence of patch test data for LAs other than lidocaine and benzocaine. Despite limited data power, stratification of variables from the MOAHLFA index suggested that the proportion of patients with leg ulcers was higher among those with benzocaine or lidocaine allergy than among dermatitis patients in general (Table 1). This finding is in accordance with previous reports (26), and is explained by the relatively frequent use of LAs in the treatment of leg ulcers. However, the possibility cannot be ruled out that some cases are explained by cross-reactivity to parabens, as topical products used for the treatment of ulcers may contain parabens, which can also result in contact allergy. Finally, concomitant exposure and allergy to parabens and LAs may also be present.

Taken together, the findings of this study show that benzocaine and lidocaine allergy is infrequent in Danish dermatitis patients from a tertiary referral patch test centre. Lidocaine should only be used for aimed testing, and we consider that benzocaine should be removed from the baseline series used in Denmark. There is currently a need for more epidemiological data from other European centres to build a platform for further discussion.

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