

Patch-Test Reactions to Topical Anesthetics: Retrospective Analysis of Cross-Sectional Data, 2001 to 2004

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Background: Allergy to topical anesthetics is not uncommon. The cross-reactivity among topical anesthetics and the screening value of benzocaine alone are not well understood.

Objectives: The goals for this study were: (1) to evaluate the frequency and pattern of allergic patch-test reactions to topical anesthetics, using North American Contact Dermatitis Group (NACDG) data, and (2) to compare these results to allergen frequencies from other published studies.

Methods: The NACDG patch-tested 10,061 patients between 2001 and 2004. In this analysis patients were included who had positive patch-test reactions to one or more of the following: benzocaine, lidocaine, dibucaine, tetracaine, and prilocaine.

Results: Of patch-tested patients, 344 (3.4%) had an allergic reaction to at least one anesthetic. Of those, 320 (93.0%) had an allergic reaction to only one topical anesthetic. Overall, reactions to benzocaine (50.0%, 172 of 344) were most prevalent, followed by reactions to dibucaine (27.9%, 96 of 344); however, reactions to dibucaine were significantly more frequent in Canada than in the United States (relative risk [RR], 2.31; 95% confidence interval [CI], 1.67–3.20; $p < .0001$). Of patients reacting to more than one anesthetic, most (79%, 19 of 24) reacted to both an amide and an ester.

Conclusions: Of the topical anesthetics tested, benzocaine was the most frequent allergen overall. Over 50% of allergic reactions to topical anesthetics in this study would have been missed had benzocaine been used as a single screening agent. Cross-reactivity patterns were not consistent with structural groups.

ON THE BASIS OF STRUCTURAL similarities, local anesthetics are divided into esters and amides. Benzocaine, tetracaine, cocaine, pramoxine, piperocaine, and proparacaine are esters. Amide anesthetics include dibucaine, lidocaine, and prilocaine. In general, ester anesthetics are considered to be more allergenic than amide anesthetics.¹ Evidence from Europe suggests that there may be little cross-reactivity between and even among these two groups of topical anesthetics.^{2–5} Some studies have also reported that allergy to dibucaine is at least as common as allergy to benzocaine and that benzocaine may not be an adequate screening agent for allergy to topical anesthetics.^{2,4}

The North American Contact Dermatitis Group (NACDG) has collected aggregated data from patients patch-tested in the United States and Canada from 1971 to the present. The caine mix was tested from 1971 to 1976; the frequency of allergic reactions ranged between 8.4 and 10.7% during that time.⁶ Benzocaine was tested as a single

screening antigen from 1984 until 2001, during which time the prevalence of allergy to benzocaine ranged from 1.7 to 3.5%.^{7–12} Beginning in 2001, the NACDG standard series was expanded to include tetracaine, lidocaine, dibucaine, and prilocaine.

The objectives for this study were (1) to evaluate the frequency and pattern of allergic patch-test reactions to topical anesthetics, using NACDG data, and (2) to compare these results to allergen frequencies from other published studies.

Materials and Methods

Between January 1, 2001, and December 31, 2004, 10,061 patients were patch-tested with the NACDG standard series of 65 allergens.^{13,14} The 2001–2002 series included benzocaine, lidocaine, dibucaine, tetracaine, and prilocaine. Prilocaine was not included in the 2003–2004 series as it accounted for only 0.1% of positive reactions during the 2001–2002 study period. Patch testing methods, relevance of reactions, and final diagnoses were determined according to methods previously reported.¹³ At a

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central location, all data were manually entered into a computerized database using *Access 2003* software (Microsoft Corporation, Redmond, WA) and checked for quality assurance. This analysis includes only patients with positive allergic patch-test reactions to one or more of the following: benzocaine, lidocaine, dibucaine, tetracaine, and prilocaine. Irritant reactions ($n = 34$) and doubtful reactions (macular erythema, $n = 65$) were excluded. A subanalysis of positive reactions by location of testing (Canada vs the United States) was also conducted with Pearson chi-square tests with one degree of freedom and Fisher's exact test (when appropriate) with SAS software (SAS Institute, Cary, NC). Previously published data from 13 patients patch-tested at the Cleveland Clinic from 2001 to 2004¹⁵ were also included in this analysis.

Results

Of the 10,061 patients patch-tested by members of the NACDG between 2001 and 2004, 344 (3.4%) had one or more allergic reactions to topical anesthetics; 134 (39.0%) were men, 210 (61.0%) were women, and 109 (31.7%) were considered atopic (hay fever, asthma, and/or eczema). The average age was 53.5 years. Of these 344 patients, 320 (93.0%) had allergic reactions to only one topical anesthetic. Overall, benzocaine (50.0%, 172 of 344) was most prevalent, followed by dibucaine (27.9%, 96 of 344) (Tables 1 and 2). Only 24 (7.0%) patients had allergic reactions to more than one anesthetic; 19 patients had reactions to anesthetics from both the amide and ester groups (Table 3). Five patients reacted to both esters tested, and only two patients reacted to all three amides tested. There was a statistically significant relationship between the geographic location of patch testing and the specific anesthetic allergy (Table 4). Patients patch-tested in Canada were only 0.7 times as likely to react to benzocaine as were patients patch-tested in the United

States (95% CI, 0.54–0.93). Conversely, patients patch-tested in Canada were 2.3 times more likely to react to dibucaine as were patients patch-tested in the United States (95% CI, 1.67–3.20).

Discussion

In this retrospective analysis of NACDG data, reactions to benzocaine were most common overall, followed (in order) by reactions to dibucaine, lidocaine, tetracaine, and prilocaine. Over 90% of patients reacted to only one topical anesthetic. Of patients reacting to more than one anesthetic, most (19 of 24, 79%) reacted to both an amide and an ester. This suggests that multiple sensitivities cannot be predicted on the basis of structural groups alone. If benzocaine is used as a single screening agent, allergy to other anesthetics may be missed.

The overall prevalence of allergy to benzocaine among all patients patch-tested was higher in our data (1.7 to 3.5%) than in reports from the United Kingdom (0.4 to 0.6%),^{3,4} and allergy to benzocaine was almost twice as prevalent as dibucaine. Among 3,000 consecutive patients patch-tested by Beck and Holden, 84 (2.8%) had positive reactions to caine mix (benzocaine, tetracaine, and dibucaine). Forty of these patients were patch-tested with the individual constituents of caine mix; among these 40 patients, Beck and Holden reported that allergy to benzocaine was more frequent than allergy to dibucaine (47.5% vs 30%, significance not reported).³ Ninety-one, (1.7%) of 5,464 patients patch-tested by Sidhu and colleagues had allergic reactions to caine mix (benzocaine, tetracaine, and dibucaine) and 54 patients were subsequently tested to constituents of the mix. Unlike Beck and Holden, Sidhu and colleagues found that allergy to dibucaine was more common than allergy to benzocaine (46.6% vs 37.9% [calculated], significance not reported).⁴ Among 1,981 patients patch-tested by Wilkinson and colleagues with 25% caine mix (1,475 patients; benzocaine, procaine, tetracaine, prilocaine, dibucaine, and lidocaine) and 15% caine mix (506 patients; benzocaine, procaine, tetracaine, prilocaine, and dibucaine), 26 (1.3%) patients reacted. Thirteen patients were tested with the individual constituents of the caine mix. As in the study by Sidhu and colleagues, allergy to dibucaine was found to be more common than allergy to benzocaine (46.7% vs 33.3% [calculated], significance not reported).²

The overall prevalence of allergy to lidocaine shown by our data (0.6%) was similar to that found by Weightman and Turner (approximately 0.3 to 0.7% [calculated]).¹⁶ Between 1972 and 1985, they reported 18 patients (0.3%,

Table 1. Patients with Positive Patch-Test Reactions to at Least One Topical Anesthetic

<i>No. of Topical Anesthetics Causing Positive Reaction</i>	<i>No. of Patients (%)</i>
Only one	320 (93.0)
Any two	18 (5.2)
Any three	4 (1.2)
Any four	2 (0.6)
All five	0 (0.0)
Total	344

Table 2. Relevance of Reactions to Topical Anesthetics

<i>Anesthetic</i>	<i>Total patients with Positive Reactions (n = 344)*</i>	<i>Relevance[†]</i>					
		<i>Definite</i>	<i>Probable</i>	<i>Possible</i>	<i>Past</i>	<i>Unknown</i>	<i>NA</i>
Benzocaine	172 (50.0%)	8	23	29	29	82	1
Dibucaine	96 (27.9%)	7	8	4	24	51	2
Lidocaine	66 (19.2%)	4	5	15	9	32	1
Tetracaine	38 (11.1%)	0	2	7	5	22	2
Prilocaine	4 (2.3%)	0	0	2	1	1	0

NA = not applicable.

**n* = 174 for prilocaine.

[†]Relevance definitions are as follow: Definite = positive use test or patch-test reaction to object or product known to contain putative allergen; Probable = putative allergen verified to be present in known skin contactant that fits clinical distribution of dermatitis; Possible = patient is exposed to circumstances in which skin contact with materials known to contain the putative allergen likely occurred; Past = past exposure to putative allergen; Unknown = unknown relevance.

Table 3. Observed Reaction Patterns

<i>Esters</i>		<i>Amides</i>			<i>No. of Patients*</i>
<i>Benzocaine</i>	<i>Tetracaine</i>	<i>Lidocaine</i>	<i>Dibucaine</i>	<i>Prilocaine</i>	
+					156
	+				27
		+			54
			+		81
				+	2
+	+				3
+		+			6
+			+		5
+	+		+		2
	+		+		2
	+	+	+		2
	+	+	+	+	2
		+	+		2
					(Total: 344)

*Nineteen patients reacted to at least one amide and at least one ester anesthetic.

Table 4. Patch-Test Reactions, by Country

<i>Anesthetic</i>	<i>Canada (n = 101)*</i>	<i>United States (n = 243)[†]</i>	<i>p-Value; RR; 95% CI</i>
Benzocaine	39 (38.6%)	133 (54.7%)	.007; 0.71; 0.54–0.93
Dibucaine	47 (46.5%)	49 (20.2%)	< .0001; 2.31; 1.67–3.20
Lidocaine	15 (14.9%)	51 (21.0%)	NS
Tetracaine	11 (10.9%)	27 (11.1%)	NS
Prilocaine	2 (4.3%)	2 (1.6%)	NS

CI = confidence interval; *n* = total number of patients with allergic reactions to topical anesthetic; NS=not statistically significant; RR = relative risk.*For prilocaine, *n* = 47.[†]For prilocaine, *n* = 127.

$n \approx 5,600$) who had positive patch-test reactions to 2% lidocaine (Warren Weightman, personal communication, November 2006). Between 1990 and 1996, they reported 11 patients (0.7%, $n \approx 1,400$) who had positive patch-test reactions to 15% lidocaine (Warren Weightman, personal communication, November 2006). In their publication, Weightman and Turner reviewed 11 patients with positive patch-test reactions to lidocaine who had reactions to one or more other amide anesthetics.¹⁶ In contrast, of our patients who reacted to lidocaine and one or more other anesthetics ($n = 12$), 6 (50%) reacted to lidocaine and an ester anesthetic (benzocaine), 4 (33%) reacted to lidocaine and both an ester and another amide anesthetic, and 2 (17%) reacted to lidocaine and another amide anesthetic. Our results support data published by Beck and Holden, Wilkinson and colleagues, and Sidhu and colleagues that suggest the lack of cross-reactivity based on ester and amide groups.²⁻⁴ Thirty-four (85%) of 40 patients patch-tested by Beck and Holden,³ 11 (85%) of 13 patients patch-tested by Wilkinson,² and 49 (84%) of 58 patients patch-tested by Sidhu and colleagues⁴ with individual components of a caine mixture reacted to only one topical anesthetic.

The differences in the rates of positive patch-test reactions to anesthetics that were reported in other publications may be due to variations in the availability and use of these drugs in different countries. In their report, Sidhu and colleagues stated that, as compared to benzocaine, approximately three times as many units of dibucaine are sold in the United Kingdom for the treatment of hemorrhoids.⁴ In the United States, there are at least 20 different over-the-counter (OTC) sources of lidocaine.¹⁵ In an informal review of a popular American online drugstore (<www.drugstore.com>, accessed February 13, 2007), common OTC sources of topical anesthetics included medications for the treatment of oral sores (benzocaine) and sunburn (lidocaine). Dibucaine appeared to be less common but was found as an ingredient in one OTC hemorrhoid treatment, Nupercainal (Novartis Consumer Health, Basel, Switzerland). A DRUGDEX (Thomson Micromedex, Greenwood Village, Colorado) trade name list for dibucaine contained 43 products; however, only Nupercainal ointment and suppositories and the generic form (dibucaine 1% ointment) could be verified as available in the United States. In Canada, in addition to OTC Nupercainal, common sources of dibucaine exposure are the prescription medication Proctosedyl (Axcan Pharma, Quebec, Canada) and its generic equivalent, which are available as ointments or suppositories for the

treatment of hemorrhoids. This informal internet search suggests that, unlike in the United Kingdom and Canada, dibucaine may be less commonly available in the United States. These findings support our results, which show that allergy to dibucaine is statistically significantly higher than allergy to benzocaine in Canada as compared to the United States. The reaction rates to lidocaine, tetracaine, and prilocaine, however, were not associated with testing location. Lidocaine is frequently used as a local anesthetic for minor surgical procedures in hospitals and clinics in both the United States and Canada. Similarly, tetracaine is used in prescription ophthalmic and intranasal medications whereas prilocaine is often used for dental anesthesia and in combination with lidocaine in the topical anesthetic cream EMLA (Astra Zeneca, Wilmington, DE).

It has been recommended that positive patch-test reactions to local anesthetics be verified with intradermal testing.¹⁷ Results of intradermal testing, if performed, were not collected as part of this NACDG database, but data from one participating center have been published. Amado and colleagues reviewed 16 patients with positive patch-test reactions to lidocaine who were seen at the Cleveland Clinic between 2001 and 2005 (13 patients patch-tested between 2001 and 2004 were also included in this publication). Intradermal tests with lidocaine 1%, mepivacaine 2%, and bupivacaine 0.5% were also performed in eight of these patients. Of these eight patients, only three had positive intradermal test reactions to lidocaine; one of these three also reacted to mepivacaine.¹⁵ The discordance between the results of patch testing and intradermal tests confirms the need to determine the relevance of positive patch-test reactions in each case. The relevance of positive patch-test reactions to anesthetics in our patients was unknown approximately 50% of the time. This suggests that, similar to reactions to thimerosal or sodium gold thiosulfate, reactions to local anesthetics may be of unclear clinical relevance.

Conclusions

Overall, benzocaine was the most prevalent anesthetic allergen in this study, but benzocaine as a single screening agent for allergy to topical anesthetics would have missed over 50% of allergic reactions to topical anesthetics. The current (2005–2006) NACDG standard series contains benzocaine, dibucaine, lidocaine, and tetracaine although this is likely to change over time.

If clinical suspicion for anesthetic allergy is high, testing with all relevant anesthetics is recommended as there

appears to be little (if any) cross-reactivity based on structure indicated by our data. Allergens chosen for patch testing should be directed by patient exposure. Other topical anesthetics not on the NACDG standard series include pramoxine, procaine, oxybuprocaine, proxymetacaine, and proparacaine, all of which may rarely cause allergic contact dermatitis. If routine patch testing is done with a smaller screening series than the NACDG standard series, benzocaine, dibucaine, and lidocaine are recommended because exposure to these allergens is common in North America.

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