

Cross-reactions among Parabens, para-Phenylenediamine, and Benzocaine: A Retrospective Analysis of Patch Testing

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Background: Parabens are alkyl ester derivatives of para-hydroxybenzoic acid and are the most commonly used preservatives in the cosmetic industry. Cross-reactions with para-amino compounds, namely, benzocaine and para-phenylenediamine (PPD), have been reported but are thought to be extremely rare.

Objective: To evaluate the rate of cross-reactivity between parabens, PPD, and benzocaine in a population of patients patch-tested in a hospital-based contact dermatitis clinic.

Methods: A retrospective analysis of 4,368 patients consecutively patch-tested between July 1989 and June 2005.

Results: Our study demonstrated that the rate of cross-reactions to parabens in PPD- and benzocaine-positive patients combined is 2%.

Conclusion: This cross-reaction rate is significant in the tested population but still falls within the previously reported rates of sensitivity to parabens in the general population (0 to 3.5%).

PARABENS are alkyl ester derivatives of para-hydroxybenzoic acid and include methylparaben, ethylparaben, butylparaben, benzylparaben, and propylparaben. They are the most commonly used preservatives in the pharmaceutical and cosmetic industries and are often combined to enhance their antimicrobial properties.^{1,2} The rates of sensitization to parabens vary from 0 to 3.5% in the general population³; however, this number tends to be higher in populations with chronic leg ulcers and chronic dermatitis.¹ Cross-reactions with para-amino compounds, namely, benzocaine and para-phenylenediamine (PPD), have been reported^{4,5} but are thought to be extremely rare. We conducted a retrospective analysis of patch testing in 4,368 patients to investigate potential cross-reactivity among parabens, benzocaine, and PPD.

Materials and Methods

At the Contact Dermatitis Clinic of the Royal Victoria Hospital (part of the McGill University Health Centre), 4,368 patients with eczematous skin disease were patch-

tested from July 1989 to June 2005. Various standard series were used during these years, including TRUE Test (Pharmacia AB, Hillerød, Denmark), the European Standard series, the North American standard series, and the North American Contact Dermatitis Group standard series (all from Chemotechnique Diagnostics, Malmö, Sweden). All of these series contained paraben mix, PPD, and benzocaine. In the TRUE Test system, paraben mix consists of equal parts of methyl-, ethyl-, propyl-, butyl-, and benzyl-4-para-hydroxybenzoate, for a total of 1,000 µg/cm². The paraben mix manufactured by Chemotechnique contains 4% each of methyl-, ethyl-, propyl-, and butyl-4-hydroxybenzoate in petrolatum, for a total of 16%. Allergens were applied on Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) and secured with Scanpor tape (Alpharma Norgesplaster A/S, Vennesla, Norway). The test materials were placed on the patient's upper back and were left for 2 days. Reactions were read after 48 and 96 hours. Patch tests were scored according to International Contact Dermatitis Research Group guidelines⁶ and were recorded in standardized fashion. Patch-test records were reviewed, and all patients with positive reactions to paraben mix, PPD, or benzocaine were included in the study. Reactions reported as doubtful ($n = 2$) were excluded from data analysis. A two-tailed Fisher exact test was used to evaluate the associations between paraben and PPD allergy with SAS (Statistical Analysis System, SAS Institute Inc., Cary, NC).

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Results

Among patients sensitized to PPD, benzocaine, and paraben mix, women outnumbered men in ratios of 1:3.2, 1:2.7, and 1:4.6, respectively. The vast majority of reactions were graded + or ++. However, among the patients who reacted positively to PPD, 67 (27%) had +++ reactions whereas only 2 (6%) of the paraben-sensitive patients and 1 (3%) of the benzocaine-allergic individuals presented with such strong reactions.

Of the 4,368 patients, 253 (5.7%) were patch-test positive to PPD, 37 (0.8%) were patch-test positive to benzocaine, and 34 (0.7%) were patch-test positive to the paraben mix (Table 1). Of the 253 PPD-positive patients, 23 (9%) also had positive reactions to benzocaine and 6 (2.37%) had positive reactions to parabens (Tables 2 and 3).

Tests of the association between parabens and PPD allergy revealed that whereas 6 (2.37%) of the 253 PPD-positive patients were sensitized to parabens, only 28 (0.68%) paraben-positive individuals were among the 4,115 PPD-negative patients. Thus, patients allergic to PPD are 3.49 times more likely to have positive reactions to parabens when compared with patients who are not allergic to PPD ($p = .012$; 95% confidence interval [CI], 1.46–8.34).

Seen from another angle, 6 (17.65%) of 34 paraben-sensitive patients were PPD positive whereas only 247 (5.7%) of the 4,334 paraben-negative patients were allergic to PPD. Patients who are allergic to parabens are 3.1 times more likely to have positive reactions to PPD than patients who are not allergic to parabens ($p = .012$; 95% CI, 1.48–6.47).

None of the 37 benzocaine-positive patients had reactions to the paraben mix; however, 2 (8.6%) of the 23 patients who reacted positively to both PPD and benzocaine were sensitive to parabens.

Discussion

The cross-reactivity among various para-amino compounds such as PPD, benzocaine, para-aminobenzoic acid

Table 2. Rates of Sensitivity to Benzocaine and Paraben Mix in Patients with Positive Reactions to para-Phenylenediamine

<i>Tested Material</i>	<i>Test-Positive Patients</i>
Benzocaine	23 (9%)
Parabens	6 (2.37%)
Total PPD-positive patients	253 (100%)

PPD = para-phenylenediamine.

(PABA), and sulfonamides has been well established. We found that 9% of PPD-positive patients also reacted to benzocaine. This cross-reaction rate is slightly lower than that reported by other authors.^{7,8} Rietschel and Fowler reported that about 25% of benzocaine-sensitive patients are also sensitive to PPD and other para-amino compounds.⁷ They suggest that the cross-reaction rates between benzocaine and PPD are not predictable and that a positive test result for benzocaine with a negative test result for PPD suggests that a broad sensitization is unlikely. Sidhu and colleagues found that about 14% of benzocaine-sensitive individuals are also sensitive to PPD.⁸

In our study, more women than men were sensitized to PPD, benzocaine, or paraben mix. This represents a population referral bias as 66% of all tested individuals were women. However, the predominance of women in the PPD-sensitive group (4.6 women for each man) reflects the fact that women have a greater exposure to this compound.

There has been a long-standing uncertainty about the cross-reactivity of parabens with the para-amino compounds. This uncertainty stems from the similar biochemical structures of the two groups of compounds: parabens have a hydroxyl group instead of an amino group in the para position. In a man with previous positive patch-test reactions to PPD, parabens, and benzocaine, Foti and colleagues described severe genital dermatitis after he used a condom containing a “retarding” cream whose ingredients included both benzocaine and parabens.⁴ Rietschel and Fowler reported several unpublished cases of positive patch-test reactions to parabens, PABA, and PPD that appeared to be true cross-reactions.⁵

Table 1. Rates of Positive Reactions to para-Phenylenediamine, Benzocaine, and Paraben Mix in 4,368 Consecutively Patch-Tested Patients

<i>Tested Material</i>	<i>Reactions</i>			<i>Total</i>	<i>Male</i>	<i>Female</i>
	+	++	+++			
PPD	83	103	67	253 (5.7%)	60	193
Benzocaine	17	19	1	37 (0.8%)	10	27
Paraben mix	19	13	2	34 (0.7%)	6	28

PPD = para-phenylenediamine.

Table 3. Patient Characteristics and Patch-Test Reactions to Paraben Mix in Patients with Positive Reactions to para-Phenylenediamine

Patient No.	Occupation	Gender	Site of Dermatitis	Positive Reactions		
				PPD	Paraben Mix	Benzocaine
3	Teacher	M	Knee brace and wrist	++	++	++
184	Housewife	F	Neck and axillae	+	+	—
192	Retired nurse	F	Eyelids	++	++	++
207	Hairdresser	F	Hands	+	++	—
223	Beautician	F	Hands	+++	++	—
295	Hairdresser	F	Hands and wrists	+	+	—

F = female; M = male; PPD = para-phenylenediamine.

In the third edition of his textbook, Fisher states the following: “Rudzki and Kleniewska point out that some authorities (eg, Paschoud) include the parabens (esters of parahydroxybenzene acid) in the “para” group, whereas others do not. In their study, Rudzki and Kleniewska found out that out of 144 paraphenylenediamine-sensitive patients, 20 were also allergic to parabens, and that out of 63 benzocaine-sensitive individuals, 20 were allergic to the parabens.”⁹ The articles by Rudzki and Kleniewska¹⁰ and by Paschoud¹¹ that are listed in “References” both have erroneous titles.¹² For example, Fisher entitles the article by Rudzki and Kleniewska “Cross Reactions between Parabens and the para Group” instead of “The Epidemiology of Contact Dermatitis in Poland” whereas Paschoud’s article is called “Cross Reactions of the para Group” when its actual title is “Tests de routine, tests composés et tests spécialisés.” In none of the articles could we find the figures quoted by Fisher. These errors have been repeated in subsequent editions, except that the reference to Paschoud’s article has been deleted. Attempts at contacting Dr. Rudzki for clarifications were unsuccessful.

Our study demonstrated that the rate of positive reactions to parabens in the PPD-sensitized patients was 2.37%, significantly higher than the rate of 0.68% found in our PPD-negative population. The rate of positive reactions to parabens was 0% in benzocaine-positive patients. When both populations are combined, the overall reaction rate to parabens is 2%. This reaction rate is still almost three times higher than in the population that had negative test results for PPD and benzocaine; however, it remains within the 0 to 3.5% range of reported paraben sensitivity rates in the general population.³

In these populations with a narrow spectrum of sensitization, the low cross-reactivity rate between parabens and para-amino compounds may be related to the different chemical ligands in the para positions of these

compounds. Hansen and colleagues reported that in human skin, the ester linkage of the parabens can be hydrolyzed to the corresponding alcohol and p-hydroxybenzoic acid (PHBA).¹³ The alcohols are not suspected sensitizers. The authors found that paraben-sensitive patients did not react to PHBA in a patch test.¹³ Therefore, the metabolic transformation of parabens may explain their low sensitization potential and decrease the risk of cross-reaction with para-amino compounds. Alternately, reactions to parabens may represent concomitant reactions and not true cross-reactions, because parabens are ubiquitous compounds exposure to which can start as early as infancy.

In the 23 patients who reacted to both PPD and benzocaine, 2 patients (8.6%) also reacted to the paraben mix. This sensitivity rate is higher than is expected in the general population and could represent true cross-reactions based on broad sensitization in these patients. However, the small number of patients in this group makes it impossible to draw valid conclusions. Combining data from larger databases could help clarify this issue.

Conclusion

Our study demonstrates that the rate of cross-reactions between the para-amino compounds and parabens is statistically significant. Whether this cross-reactivity pattern is clinically relevant or not remains to be determined.

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References

1. Cashman AL, Warshaw EM. Parabens: a review of epidemiology, structure, allergenicity, and hormonal properties. *Dermatitis* 2005; 16:57–66.
2. Sasseville D. Hypersensitivity to preservatives. *Dermatol Ther* 2004; 17:251–63.
3. Fransway AF. Preservatives. In: Guin JD, editor. *Practical contact dermatitis, A handbook for the practitioner.*, New York: McGraw-Hill; 1995. p. 539–58.
4. Foti C, Bonamonte D, Antemi A, et al. Allergic contact dermatitis to condoms: description of a clinical case and analytical review of current literature. *Immunopharmacol Immunotoxicol* 2004;26:481–5.
5. Rietschel RL, Fowler JF Jr. Allergy to preservatives and vehicles in cosmetics and toiletries. In: Rietschel RL, Fowler JF Jr, editors. *Fisher's contact dermatitis*, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 211–59.
6. Wilkinson DS, Fregert S, Magnusson B, et al. Terminology of contact dermatitis. *Acta Derm Venereol* 1970;50:287–92.
7. Rietschel RL, Fowler JF Jr. Local anesthetics. In: Rietschel RL, Fowler JF Jr, editors. *Fisher's contact dermatitis*. 4th ed. Philadelphia: Williams & Wilkins; 1995. p. 236–48.
8. Sidhu SK, Shaw S, Wilkinson JD. A 10-year retrospective study on benzocaine allergy in the United Kingdom. *Am J Contact Dermat* 1999;10:57–61.
9. Fisher AA. Dermatitis to preservatives and other additives in cosmetics and medications. In: Fisher AA, editor. *Contact dermatitis*, 3rd ed. Philadelphia: Lea & Febiger; 1986. p. 240.
10. Rudzki E, Kleniewska D. The epidemiology of contact dermatitis in Poland. *Br J Dermatol* 1970;83:543–5.
11. Paschoud JM. Tests de routine, tests composés et tests spécialisés. *Dermatologica* 1968;136:193–214.
12. Fisher AA. Dermatitis to preservatives and other additives in cosmetics and medications. In: Fisher AA, editor. *Contact dermatitis*. 3rd ed. Philadelphia: Lea & Febiger; 1986. p. 255.
13. Hansen J, Mollgaard B, Avnstorp C, Menne T. Paraben contact allergy: patch testing and in vitro absorption/metabolism. *Am J Contact Dermat* 1993;2:78–86.