Immediate Hypersensitivity to Methylparaben Causing False-Positive Results of Local Anesthetic Skin Testing or Provocative Dose Testing

By Eric Macy, MD
Michael Schatz, MD, MS
Robert S Zeiger, MD, PhD

Presented at the 58th annual meeting of the American Academy of Allergy, Asthma and Immunology, New York, NY, March 3, 2002, and published in abstract form in: J Allergy Clin Immunol 2002 Jan;109(1 Suppl):S149.

Abstract

Background: Parabens are widely used preservatives in food, cosmetics, and drugs, including many amide-type local anesthetic (LA) agents. Although parabens have been associated with delayed contact sensitivity, immediate hypersensitivity reactions rarely result from parenteral exposure to parabens and even less commonly result from mucosal or cutaneous exposure. In addition, immediate hypersensitivity rarely results from use of amide-based LA agents administered in pure form (ie, prepared without preservatives).

Objective: Analyze outcome data from LA skin testing (ST) and provocative dose testing (PDT) administered during a 16-year period; and present the history in three initially LA ST-positive cases, one of which proved to be related to methylparaben.

Methods: Results of all LA ST or PDT done in a large HMO allergy practice caring for 285,000 to 510,000 people in Southern California from August 13, 1985 through August 7, 2001 were reviewed.

Results: Of 287 patients who had amide-type LA ST or PDT done initially, 252 received the LA agent preserved with methylparaben. Three patients demonstrated a positive ST reaction to lidocaine preserved with methylparaben. All three had a negative ST or PDT reaction to pure LA agents. These agents included lidocaine. One patient, who had a history of immediate hypersensitivity reaction when exposed orally to parabens in foods, had a positive reaction to subsequent ST with pure methylparaben. No patient had a positive reaction to ST or PDT using amide-type LA agents.

Conclusions: Local anesthetic ST or PDT is a safe procedure, and immediate hypersensitivity to pure amide LA agents is extremely rare. Methylparaben was the only established cause for an immediate hypersensitivity reaction during LA ST identified in a large allergy practice during the past 16 years.

Introduction

Parabens are widely used as preservatives in cosmetics, foods, and drugs. Parabens have been extensively studied and are safe as currently used.[1] They are commonly encountered as preservatives in multidose vials of amide local anesthetic (LA) agents. Parabens noncovalently denature proteins through their phenol moiety and haptinate proteins through their benzoic acid moiety. Rarely, patients can become immunologically sensitized to parabens. Methylparaben, one of the most commonly used parabens, is a well-documented cause of T-cell-mediated contact sensitivity.[2] One case report documented a urticarial maculopapular rash which resulted 36 hours after ingestion of a haloperidol solution containing methylparaben.[3] Methylparaben has only rarely been reported to cause immediate hypersensitivity, even after parenteral exposure.[4-7] Most of the documented cases of immediate hypersensitivity to methylparaben have been verified by a positive skin test (ST) result, but positive passive transfer (Prausnitz-Kustner) test reactions

Methylparaben, one of the most commonly used parabens, is a well-documented cause of T-cell-mediated contact sensitivity.

Eric Macy, MD, (top), works in the Department of Allergy in the San Diego Medical Center, as well as being a Partner Physician with the Southern California Permanente Medical Group, and an Assistant Clinical Professor of Medicine at the University of California, San Diego. E-mail: eric.m.macy@kp.org.
Michael Schatz, MD, MS, (left), has been at Kaiser for 25 years and is currently Chief of the Department of Allergy in San Diego. He is also Clinical Professor in the Department of Medicine, University of California San Diego School of Medicine and currently Vice-President of the American Academy of Allergy Asthma and Immunology. E-mail: michael.x.schatz@kp.org.
Robert S Zeiger, MD, PhD, (right), served for 24 years as Chief of Allergy at the Kaiser Permanente Medical Center in San Diego and recently transitioned to Senior Physician Investigator and Director of Allergy Research. He also is Clinical Professor of Pediatrics at the University of California, San Diego. E-mail: robert.s.zeiger@kp.org.

Table 1. Reaction to local anesthetic preparations used for skin testing (ST) and for provocative dose testing (PDT)

Preparation	No. of subjects tested	No. (%) of subjects with adverse reaction reported despite negative PDT result	No. of subjects with positive test result	
			ST	PDT
1% or 2% lidocaine/0.1% methylparaben	232	19 (8.2)	3[a]	0
1% mepivacaine/0.1% methylparaben	18	3 (16.6)	0	0
1% bupivacaine/0.1% methylparaben	2	0 (0)	0	0
Totals for preparations containing methylparaben	252	22 (8.7)	3 (1.2)	0 (0)
1% or 2% lidocaine	22	1 (4.5)	0	0
4% prilocaine	6	0 (0)	0	0
2% mepivacaine	8	2 (25.0)	0	0
Totals for local anesthetic agents without preservatives	35	4 (8.6)	0 (0)	0 (0)

[a]These patients had dose testing using anesthetic preparations without preservatives and include two patients with positive result of prick puncture and one patient with positive result of intradermal dose testing.

We reviewed the results of all LA agent PDT done … 85,000 to 510,000 people in Southern California from August 7, 2001.

have also been reported.[8]

Reports are rare of well-documented positive ST or provocative dose testing (PDT) results to amide LA agents in patients evaluated for possible clinical reactions to LA agents. LA testing is routinely done using multidose vials of LA agents containing methylparaben as a preservative. Some reported (but poorly documented) positive ST or PDT reactions to amide LA may in fact be reactions to methylparaben and not to LA agents. The present report confirms that methylparaben is responsible for at least some of the positive ST or PDT results in patients tested with amide LA agents.

Methods

We reviewed the results of all LA agent ST and PDT done in a large HMO allergy practice providing all of the allergy consultative services for 285,000 to 510,000 people in Southern California from August 13, 1985 through August 7, 2001. This study was reviewed and approved by the Southern California Kaiser Permanente Institutional Review Board.

ST with LA agents was done on the forearm, and PDT was done on the upper lateral arm. A negative saline control, a positive 0.1%-histamine control, and an initial undiluted LA prick puncture (PP) test were placed and read at 20 minutes. A wheal 3 mm greater than the saline control was considered a positive test result. If the PP test result was negative, the histamine control positive, and the saline control negative, then an intradermal (ID) test using 0.04 mL of a 1:100 dilution of the LA agent was placed along with the saline and 0.01%-histamine controls. These tests were read at 20 minutes and, if negative, a single-blind placebo, 1-mL subcutaneous injection of saline was administered. If the placebo challenge was negative after 20 minutes, then a 1-mL subcutaneous injection of an undiluted LA agent was administered, and the patient was observed for 20 minutes.

The placebo or active-drug PDT was considered positive if the patient had a positive wheal-and-flare reaction at the site of undiluted LA administration, any acute-onset pruritic rash distant from this site, 15% decrease in blood pressure, wheezing, or 15% decrease in FEV^1 of pulmonary function occurring during the 20-minute posttest observation period. Only objectively observed adverse reactions reported during the performance of the placebo or active-drug PDT were considered positive challenges.

A 1% or 2% solution of lidocaine with 0.1% methylparaben was the material most commonly used for ST or PDT. A 1% solution of mepivacaine with 0.1% methylparaben was the second most commonly used material containing methylparaben. A pure 1% or 2% solution of lidocaine was the most commonly used LA agent that did not contain methylparaben. Other LA agents with and without preservatives were selected for use on the basis of the patient's clinical history or by request of the patient or referring physician. Some patients had ST or PDT with more than one LA agent or with the same preparation more than once. Some of the additional tests used to further characterize reactivity of the three initially ST-positive patients were limited to puncture and intradermal ST. Epinephrine-containing materials were not used for any testing.

Results

Of the 287 patients who had at least one LA ST or PDT, 253 patients were exposed to lidocaine. Mean age of patients at initial testing was 47.8 ± 19.1 years (range, 3.9 to 91.9 years). The cohort included 220 (76.7%) women and 67 (23.3%) men. Of subjects tested, 252 (87.8%) were also exposed to 0.1% methylparaben. Table 1 lists the amide LA agents used for routine ST or PDT and the results of the tests. Table 2 lists the 25 subjectively perceived adverse reactions reported. Of these reported adverse reactions, 22 (88%) occurred in women, and 3 (12%) occurred in men. Fourteen

patients had ST or PDT more than once. All patients who had LA ST or PDT more than once had a negative result on all tests except as noted in one of the three initially ST-positive patients. All three initially ST-positive patients subsequently tolerated PDT with pure lidocaine. No objective clinical signs of adverse reaction—including pruritic rash at the site of injection, distant pruritic rash or urticaria, wheezing, or hypotension—occurred in any patient during PDT.

Table 3 presents the additional immediate hypersensitivity ST results for the three patients who initially tested positive to lidocaine with methylparaben. Clinical histories of these patients are presented.

Case Reports

The patient in Case 1 was a 39-year-old man initially seen in the allergy department in 1994 with the chief complaint of adult-onset "food allergy" to ice cream. He also had a four-year history of immediate-onset burning, itching, swelling, redness, and pain after topical exposure to many shampoos and lotions. The cutaneous symptoms would start clearing within ten minutes if he completely removed the offending materials from his skin. He had no clinical signs of delayed contact sensitivity and no fixed eruptions or blistering rashes. The most problematic food was a particular brand of "pralines and cream" ice cream. Eating the ice cream caused immediate-onset oropharyngeal swelling, change in tone of his voice, and mild shortness of breath. He could drink milk and eat the other protein-containing materials in the ice cream, such as eggs and nuts, without any problem. The patient had no history of physical or idiopathic urticaria. Cold urticaria was ruled out by negative results of an ice cube test administered at the initial visit, and plans were made to give the patient a skin test with the constituents of the implicated ice cream. The patient failed to follow up with the rest of the evaluation. The patient next came to the clinic 51 months later with a new complaint of severe oral and facial swelling with the use of an over-the-counter topical oral benzocaine preparation. This condition became more problematic when, during the course of dental work, he was exposed to both topical benzocaine and parenteral lidocaine and had severe immediate-onset oropharyngeal swelling but no shock or anaphylaxis. The dental work was postponed. The patient had managed his previous problems from ice cream and other materials by avoidance. He now needed dental work and needed to know what LA agent he could tolerate. The patient had tolerated LA agents before 1994 without any problem. He had no history of hay fever, asthma, or any other drug or food allergy or intolerance. He was not taking any medications.

The patient had ST and PDT to a panel of LA agents with and without preservatives. The patient reacted to all products containing methylparaben and not to any of the local anesthetics without methylparaben, even if they had other nonparaben preservatives. The patient was not rechallenged with benzocaine (Table 3). He did not react to the other ester forms of local anesthetic: procaine, cocaine, and tetracaine. The patient was given specific instructions on how to identify products containing methylparaben and obtained a Medic-Alert bracelet indicating his hypersensitivity to methylparaben. He was instructed to avoid cutaneous or mucous membrane exposure to benzocaine.

The patient in Case 2 (initially seen in 2000) was a 37-year-old, gravida 2, para 1 woman, four months pregnant, who had a history of possible allergic reaction to either penicillin or lidocaine. Fifteen years previously, the patient was treated with oral amoxicillin or penicillin for one week and with lidocaine spray for a sore throat. Twenty minutes after receiving a dose of penicillin and an unspecified time after lidocaine was sprayed into her mouth, palmar itching developed, and she fainted. She was aroused with smelling salts and was brought to the emergency department. She had cyanotic hands but no rash or respiratory difficulty. She received therapy but could not recall specific details of the allergic episode. Her symptoms resolved within a couple of hours. She had no history of allergic rhinitis, asthma, or allergy to food or insects, and her family history did not include allergic disease. The patient was well and was not taking medication. The patient was referred to the allergy department for assessment of possible allergy to lidocaine. Physical examination results were normal except for evidence of pregnancy. The patient was ST-positive to lidocaine with methylparaben and was ST- and PDT-negative to pure lidocaine (Table 4). We recommended that

Table 2. Subjectively reported adverse reactions occurring during or after administration of provocative dose tests in 249 patients who had a negative reaction to local anestheticagents containing methylparaben[a]

Adverse reaction	No. (%) of patients
Anxiety	3
Cough, sneeze, or both	2
Headache	2
Itch, no rash	3
Lightheadedness	4
Pain at injection site(s)	2
Nausea	3
Sleepiness	2
Delayed onset of adverse reaction (>24 hours) maculopapular rash at site(s) of methylparaben injection	1
Total	22 (8.8%)

[a] Lightheadedness occurred in three (8.6%) of 35 patients who had a negative reaction to pure local anesthetic agents administered in provocative dose tests.

Of these reported adverse reactions, 22 (88%) occurred in women, and 3 (12%) occurred in men.

… the much more widely used, amide group, which includes lidocaine, mepivacaine, bupivacaine, prilocaine, etidocaine, and ropivacaine.

the patient return postpartum for penicillin testing and for further testing with methylparaben, but she moved from San Diego and did not return for further evaluation.

The patient in Case 3 was a 55-year-old woman referred to the allergy clinic for evaluation of local anesthetic allergy. Fourteen months before evaluation in the allergy department, the patient did not react to dental injection of lidocaine or to latex glove exposure. Two months before evaluation in the allergy department, similar lidocaine and latex exposure was followed in the evening by an unusual sensation around her lips, followed the next day by lip swelling. One week later, latex gloves and lidocaine were again used and were again followed the next day by onset of lip swelling. The patient needed further dental work. She had a history of postpolio syndrome. She had also noticed nonpruritic skin erythema on certain occasions, such as with heat. She had no history of hay fever, asthma, or eczema. She was being treated with verapamil, estrogen, and nortriptyline. Results of an ELISA test to latex were negative.

Intradermal ST using a 1:100 dilution of lidocaine with methylparaben initially produced a positive reaction manifested by diffuse erythema of the arms and trunk without pruritus or any other signs of a systemic IgE-mediated reaction. She returned 2-1/2 weeks later to have the skin tests repeated, but nonpruritic erythema from sitting in a warm room was already apparent, and the test was deferred. Four weeks after the initial test, the patient had a negative reaction to ST with pure prilocaine and with pure lidocaine. She had a negative reaction to PDT with pure prilocaine. When the patient returned (ten weeks after the initial test), she had a negative reaction to ST with methylparaben. She next returned 17 weeks after the initial test and had negative reactions to ST/PDT with lidocaine combined with methylparaben—the same preparation to which she initially had a positive ST result (Table 3).

Table 3. Results of tests (prick puncture, intradermal, and provocative dose tests) using local anesthetic agents, preservatives, or both in patients who initially showed positive reaction to methylparaben (mm wheal/mm flare)[a]

Agent	Case 1	Case 2	Case 3
1% lidocaine/0.1% methylparaben	10/35[b] 10/30[b] 22/50[b]	5/20[b]	0/0[b] 10/25[c] 0/0[b] 0/0
1% mepivacaine/0.1% methylparaben	20/40[b]	test not done	test not done
0.5% bupivacaine/0.1% methylparaben (ester)	15/35[b]	test not done	test not done
1% procaine/0.09% metabisulfite[e]	0/0[b] 0/0[c] negative reaction[d]	test not done	test not done
0.1% methylparaben	3/40[b]	test not done	0/0[b] 0/0[c] 0/0[b] 0/0[c]
4% cocaine (ester)	0/0[b]	test not done	test not done
1% tetracaine (ester)	0/0[b]	test not done	test not done
1% etidocaine	0/0[b]	test not done	test not done
4% prilocaine	0/0[b]	test not done	0/0[b] 0/0[c] negative reaction[d]
1% lidocaine	0/0[b] 0/0[c] negative reaction[d]	0/0[b] 0/0[c] negative reaction[d]	0/0[b] 0/0[c]

[a]Read at 20 minutes; [b]prick puncture; [c]intradermal test positive; [d]provocative dose test positive;
[e]Metabisulfite is an alternative to methylparaben. All local anesthetic agents are amide unless noted otherwise.

Discussion

Depending on their chemical structure, LA agents are grouped into two categories: the ester group, which includes benzocaine, cocaine, procaine, chlorprocaine, and tetracaine; and the much more widely used, amide group, which includes lidocaine, mepivacaine, bupivacaine, prilocaine, etidocaine, and ropivacaine. The esters are derivatives of para-aminobenzoic acid and share chemical features with parabens. No epinephrine was used in the testing, because epinephrine can mask both vasodilatation and the vascular permeability associated with a positive, immediate-hypersensitivity ST result and may also cause anxiety in some patients.

In 1984, one patient who apparently had an immediate hypersensitivity reaction after mucosal exposure to methylparaben (delivered by barium enema) reportedly had a positive methylparaben ST result.[9] Despite wide use of methylparaben as a preservative in foods, beverages, and drugs, no well-defined case of immediate hypersensitivity to methylparaben has been reported for patients who had index exposure to the preservative via the oral route. One report[10] described an attempt to develop an in vitro test for IgE directed against methylparaben, but no positive sera were identified by the test. To date, no positive in vitro test for methylparaben or for amide LA-specific IgE has been reported. Little convincing information exists that amide LA agents as a class can induce clinically significant IgE production in humans.

Frequency of adverse reactions attributed to LA agents and actually caused by those agents has been reduced with widespread use of the amide type of LA agents throughout the past 30 years.[11] The patient described in Case 1 had clinical symptoms of immediate hypersensitivity after oral and cutaneous exposure both to benzocaine and to methylparaben.

Fisher and coworkers[12] presented data for 208 patients (referred during a 20-year period) who had a history of allergy to LA agents. Four of these patients had positive PDT test results, and another four patients had a delayed cutaneous reaction. Three of these eight patients were subsequently given LA agents and tolerated them well. The authors concluded that "a history of allergy to local anesthesia is unlikely to be genuine and local anesthetic allergy is rare. In most instances it can be excluded from the history and the safety of local anesthetic verified by progressive challenge."[12:abstract] Gall and coworkers[13] described 177 patients with a history of LA intolerance and found five who initially had a positive reaction to preservatives. Of 164 patients tested, the authors identified two (1.2%) who had a positive reaction to paraben PP and ST,[13] virtually the same rate identified in the present study.

Of 252 patients, we identified only one (0.4%) who had a delayed-onset rash at the PDT site of exposure to the lidocaine combined with methylparaben. This result was compatible with contact sensitivity. This patient was told to avoid methylparaben.

This study documents the need to reconfirm initially positive test results, because transient dermographism may be missed by use of the saline control. We now recommend updating the previous recommendations from Schatz[14] that lidocaine with methylparaben should be the initial material used for routine LA ST or PDT. Given the infrequency of positive test results, we would recommend repeating any positive tests not associated with clinically significant systemic reactions. If the test result remains positive, ST or PDT should be done using pure lidocaine. The person identified by this protocol as having a rare positive reaction to methylparaben can then actively avoid parabens and is unlikely to have a positive reaction to amide LA agents.

The present study confirms the rarity of positive ST or PDT results from exposure to pure amide LA agents.[11] Our experience suggests that any positive reaction to ST or PDT using LA agents with methylparaben is likely either to result from exposure to methylparaben or to represent a false-positive result.[12] Data from the present report add to the safety database of reactions to amide LA agents. Because today methylparaben is the preservative most commonly used in multidose vials, the findings presented here should raise awareness that methylparaben is a potential cause for local reactions previously attributed to the anesthetic agent itself. ❖

Practice Tips
The cutaneous symptoms of a topical allergic reaction—immediate-onset burning, itching, swelling, redness, and pain—would start clearing within ten minutes if the offending materials were completely removed from the skin.
Cold urticaria can be ruled out by negative results of an ice cube test.
Epinephrine can mask both vasodilation and the vascular permeability associated with a positive, immediate hypersensitivity skin test result.
Reconfirm initially positive test results, because transient dermographism may be missed by use of the saline control.
Methylparaben is the preservative most commonly used in multidose vials, raising awareness that methylparaben is a potential cause for local reactions previously attributed to the anesthetic agent itself.

The present study confirms the rarity of positive ST or PDT results from exposure to pure amide LA agents.

References

1. American College of Toxicology. Final report on the safety assessment of methylparaben, ethylparaben, propylparaben, and butylparaben. J Am Coll Toxicol 1984;3:147-209.
2. Rietschel RL, Fowler JE Jr. Fisher's contact dermatitis. 4th edition. Baltimore: Williams and Wilkins; 1995. p 265-8.
3. Kaminer Y, Apter A, Tyano S, Livni E, Wijsenbeek H. Delayed hypersensitivity reaction to orally administered methylparaben. Clin Pharm 1982 Sep-Oct;1(5):469-70.
4. Aldrete JA, Johnson DA. Allergy to local anesthetics. JAMA 1969 Jan 13;207(2):356-7.
5. Latronica RJ, Goldberg AF, Wightman JR. Local anesthetic sensitivity. Report of a case. Oral Surg Oral Med Oral Pathol 1969 Sep;28(3):439-41.
6. Nagel JE, Fuscaldo JT, Fireman P. Paraben allergy. JAMA 1977 Apr 11;237(15):1594-5.
7. Johnson WT, DeStigter T. Hypersensitivity to procaine, tetracaine, mepivacaine, and methylparaben: report of a case. J Am Dent Assoc 1983 Jan;106(1):53-6.
8. Henry JC, Tschen EH, Becker LE. Contact urticaria to parabens. Arch Dermatol 1979 Oct;115(10):1231-2.
9. Schwartz EE, Glick SN, Foggs MB, Silverstein GS. Hypersensitivity reactions after barium enema examination. AJR Am J Roentgenol 1984 Jul;143(1):103-4.
10. Kokubu M, Oda K, Shinya N. Detection of serum IgE antibody specific for local anesthetics and methylparaben. Anesth Prog 1989 Jul-Oct;36(4-5):186-7.
11. Eggleston ST, Lush LW. Understanding allergic reactions to local anesthetics. Ann Pharmacother 1996 Jul-Aug;30(7-8):851-7.
12. Fisher MM, Bowey CJ. Alleged allergy to local anaesthetics. Anaesth Intensive Care 1997 Dec;25(6):611-4.
13. Gall H, Kaufmann R, Kalveram CM. Adverse reactions to local anesthetics: analysis of 197 cases. J Allergy Clin Immunol 1996 Apr;97(4):933-7.
14. Schatz M. Skin testing and incremental challenge in the evaluation of adverse reactions to local anesthetics. J Allergy Clin Immunol 1984 Oct;74(4 Pt 2):606-16.