

Allergic Contact Dermatitis to Pramoxine (Pramocaine)

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Prescription and over-the-counter topical anesthetics are commonly used. Although allergy to amide and ester anesthetics is known, little has been reported on the nonamide, nonester pramoxine (pramocaine). This article briefly reviews allergy to topical anesthetics, provides detailed information on pramoxine, and describes characteristics of multiple patients with positive, relevant reactions to pramoxine.

Topical Anesthetics

Prescription and over-the-counter topical anesthetics are commonly used worldwide. These medications reversibly inhibit voltage-gated sodium channels on neurons, thereby decreasing pain signaling. Most anesthetics contain a lipophilic aromatic ring, a variable intermediate bond, and hydrophilic group. There are 3 large groups of anesthetics based on structure of the immediate group: (1) amide, (2) ester, or (3) other.¹ In North America, commonly used amide topical anesthetics include dibucaine, lidocaine, and prilocaine; commonly used esters include benzocaine and tetracaine.¹ Anesthetics not easily classified into amides and esters (“other”) include pramoxine and dyclonine (Table 1).

Type 1 Allergy to Topical Anesthetics

Type 1 allergy, characterized by urticaria, anaphylaxis, bronchospasm, angioedema, and/or hypotension, is rare, accounting for less than 1% of adverse reactions to anesthetics. This type of allergy typically occurs from nontopical exposures (ie, intradermal, intramuscular, systemic). Esters are more frequently responsible; it is speculated that this is due to the allergenic potential of *para*-aminobenzoic acid, an intermediate of ester anesthetic breakdown.² Type 1 allergy rarely occurs from topical application of anesthetics. Cross-reactivity is common within the ester and within the amide groups for type 1 allergy due to systemic exposure.³ Therefore, patients with systemic reactions to ester anesthetics are generally advised to avoid all esters. For topical exposure, however, cross-reactivity between anesthetics in type 1 allergy is unclear. Some studies suggest that there may be cross-

reactivity between topical ester anesthetics, but not between topical amide anesthetics.^{2,4}

A literature search yielded few case reports of likely/confirmed type 1 allergy caused by topically applied anesthetics. Reports include the following reactions: rapid-onset erythema and edema of the face; angioedema of the lips; localized urticaria from a lidocaine/tetracaine peel⁵; urticaria and eyelid swelling shortly after application of tetracaine ophthalmic drops⁶; and anaphylaxis requiring intubation from both a topical lidocaine spray in the oropharynx/nares⁷ and benzocaine cream applied to the lips.⁸ Tolerance of other anesthetics was not assessed in these patients with the exception of the latter case; that benzocaine-allergic patient tolerated topical prilocaine.⁸

Type 4 Allergy to Topical Anesthetics

Type 4 allergy (allergic contact dermatitis) is more common from topical anesthetics than systemic anesthetics.^{2,4} Several recent studies found that 2.0% to 4.0% of patients referred for patch testing had 1 or more positive reactions to a topical anesthetic.^{9–11} A 2012 study of 171 of patients with reactions to 1 or more topical medications found that 17% had reactions to topical anesthetics, the third most frequent medicament behind antibiotics and corticosteroids.¹²

The frequency of positive reactions to specific topical anesthetics varies by exposure. In North America, the most frequently positive topical anesthetics are benzocaine (on average 1.4%–1.6% of North American Contact Dermatitis Group patch-tested patients) and lidocaine (on average 0.8%–1.0% of North American Contact Dermatitis Group patch-tested patients).^{10,11,13} Dibucaine (cinchocaine) is commonly used in Canadian hemorrhoid preparations and is a common culprit there.¹⁴ Unlike type 1 allergy in which cross-reactivity occurs within members of the ester (or amide) group, there seem to be no consistent patterns of cross-reactivity for type 4 allergy between anesthetics within the same structural group.¹⁰ A 2008 study found that 19 of 24 patients with 2 or more positive reactions to topical anesthetics had reactions to at least 1 amide and ester.¹⁰ Given this information,

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TABLE 1. Common Topical Anesthetics in North America by Structural Class

Amide	Ester	Other
Articaine	Benzocaine	Dyclonine
Bupivacaine	Chloroprocaine	Pramoxine
Dibucaine	Cocaine	
Etidocaine	Procaine	
Levobupivacaine	Proparacaine	
Lidocaine	Tetracaine	
Mepivacaine		
Prilocaine		
Ropivacaine		

most experts recommend alternative topical anesthetics based on negative testing, not on structural group.¹⁵

Allergy to “Other” (Nonester and Nonamide) Topical Anesthetics

Allergy to topical anesthetics that do not fall into the amide or ester categories is poorly reported in the literature. These include dyclonine and pramoxine. There have been 4 reports of dyclonine allergy, 3 from topical therapies for herpes simplex and 1 from a first-aid ointment^{12,16,17}; pramoxine, or pramocaine, is a topical anesthetic found in numerous prescription and over-the-counter anti-itch and pain-relief topical preparations (Tables 2, 3). Pramoxine is most structurally similar to dyclonine, but dyclonine and pramoxine do not seem to cross-react.^{12,16} A literature search found 6 reports of contact dermatitis to pramoxine, most from more than 10 years ago (Table 4). All were type 4 allergic reactions to topical products. Culprit products included a triple antibiotic plus pain-relief ointment, Tronotene hemorrhoid ointment, Nestosyl cream, Preparation H cream, and possible sensitization by EMLA cream.^{18–21}

Our Clinic Experience

Pramoxine was previously not commercially available as a patch test preparation. We became aware of this as an allergen after a patient reacted only to his personal antibiotic ointment containing pramoxine

but not to his personal antibiotic ointment without pramoxine (all other ingredients in the 2 products were identical).²¹ After that case, we began to test for pramoxine allergy using 2 pramoxine-containing products (Nikzon and Prax Lotion). When pramoxine hydrochloride 2% petrolatum (pet.) became commercially available, this was added to our medicament series, and we have been surprised at the number of positive and clinically relevant reactions. In most cases, other factors (irritant contact dermatitis, atopic dermatitis) likely preceded sensitization to pramoxine as it is typically in products designed to treat itchy skin conditions. Cosensitization is common to neomycin and bacitracin. A convenience sample of notable cases from 2016 to 2019 is outlined hereinafter.

Patient 1

A 55-year-old woman presented with a 9-year history of hand/fingertip dermatitis (Fig. 1A). She tried several treatments including Neosporin + Pain Relief Ointment, which declared pramoxine. Because pramoxine allergy was suspected, but pramoxine was not commercially available at the time of testing, Nikzon and Prax Lotion were added at her 48-hour visit. Day 5 reading showing very strong (++++) reactions to her Neosporin ointment (Figs. 1B–D), as well as Nikzon and Prax Lotion. Other ingredients in Nikzon and Prax lotions were negative.

Patient 2

A 73-year-old man presented with an 18-year history of diffuse body dermatitis including the groin/anogenital area. He had tried several treatments including Sarna Sensitive Anti-Itch Lotion on the body as well as Preparation H Cream and Up and Up Medicated Hemorrhoid Pads in the perianal area; all declared pramoxine. Day 5

TABLE 3. Common Over-the-Counter Topical Products Containing Pramoxine

Use	Preparation	Brand Name Products*
Antipruritic	Pramoxine	CeraVe Itch Relief Moisturizing Lotion/Cream
		Sarna Sensitive Anti-Itch Lotion
		Ivarest Poison Ivy Itch Spray/Cream
	Pramoxine/calamine	Caladryl Lotion
		Aveeno Anti-Itch Concentrated Lotion
		Caladryl Clear Lotion
Hemorrhoid relief	Pramoxine/zinc acetate	Callergy Clear Lotion
		Gold Bond Rapid Relief Anti-Itch Lotion/Cream
		Preparation H Maximum Strength Cream
Antibiotic plus pain relief	Pramoxine/menthol	Neosporin + Pain Relief Cream/Ointment
Antibiotic plus pain relief	Pramoxine/bacitracin/neomycin/polymyxin B	

*Generic drugstore/big-box store brands not included.

TABLE 2. Number of Pramoxine-Containing Products on DailyMed Web Site (Accessed June 26, 2019)

Search Term	No. Products
Pramoxine	354
Human	306
Animal	48
Pramoxine/bacitracin	86
Pramoxine/zinc acetate	38
Pramoxine/calamine	27
Pramoxine/phenylephrine	34
Pramoxine/hydrocortisone acetate	21
Pramoxine/menthol	17
Pramoxine/benzyl alcohol	2

TABLE 4. Summary of Patients With Positive Reactions to Pramoxine and/or Pramoxine-Containing Products

1st Author, Year, Country (Previous Studies); Patient No. (Current Study)	Age	Sex	Location of Dermatitis	Pertinent Positive Patch Test Results	Pertinent Negative Patch Test Results	Responsible Pramoxine- Containing Product(s)	Comments
van Ketel, ¹⁸ 1981, the Netherlands	NR × 2	NR × 2	NR × 2	Strength NR: Nestosyl ointment	Nestosyl inactive ingredients, benzocaine, procaine, tetracaine, bupivacaine, mepivacaine, prilocaine, lidocaine	Nestosyl ointment	Purified pramoxine not tested
Cusano, ¹⁹ 1993, Italy	32	Female	Perianal, buttocks, upper thighs	++: Tronotene ointment	Tronotene excipients	Tronotene Ointment	Purified pramoxine not tested
Garcia, ²⁰ 2007, Spain	76	Male	Leg at site of 2-y-old ischemic ulcer	++/+++: prilocaine 5% pet., EMLA cream (lidocaine/ prilocaine); +: pramocaine 1% pet., bupivacaine 0.25% aqueous (aq.)	Mepivacaine 1% aq., articaine 4% aq., benzocaine 5% pet., procaine 1% pet., tetracaine 0.75% pet.	EMLA cream	Authors suggest cross-sensitivity between prilocaine and pramoxine given no known exposure to pramoxine
Hylwa, ²¹ 2014, United States	56	Male	Knee at site of 1-y-old surgical site wound	++: triple antibiotic ointment with pramoxine	Same triple antibiotic ointment w/o pramoxine, benzocaine, lidocaine	Maximum Strength Walgreens Triple Antibiotic with Pain Relief	Purified pramoxine not tested
Schlarbaum, ²² 2019, United States	52	Female	Anogenital area at site of recent gender reaffirming surgery	Strength NR: pramoxine, Preparation H cream	NR	Preparation H cream	
Patient 1	55	Female	Hand, fingertip	+++ : Nikzon, Prax Lotion, Neosporin + Pain Relief Ointment	Benzocaine 5% pet., lidocaine 15% pet.	Neosporin + Pain Relief Ointment	Purified pramoxine not tested
Patient 2	73	Male	Diffuse, groin, anogenital	+: Nikzon, Prax Lotion, Sarna Sensitive Anti-Itch lotion, Preparation H Cream, hemorrhoid pads	Benzocaine 5% pet., lidocaine 15% pet.	Sarna Sensitive Anti-Itch lotion, Preparation H cream, hemorrhoid pads	Purified pramoxine not tested
Patient 3	33	Male	Lower leg, dorsal foot	++: pramoxine 2% pet. +: Walgreens Calamine Plus Spray	Benzocaine 5% pet., lidocaine 15% pet.	Walgreens Calamine Plus Spray	

(Continued on next page)

TABLE 4. (Continued)

1st Author, Year, Country (Previous Studies); Patient No. (Current Study)	Age	Sex	Location of Dermatitis	Pertinent Positive Patch Test Results	Pertinent Negative Patch Test Results	Responsible Pramoxine- Containing Product(s)	Comments
Patient 4	63	Male	Diffuse	++: pramoxine 2% pet.; Sarna Sensitive Anti-Itch Lotion	Benzocaine 5% pet., lidocaine 15% pet.	Sarna Sensitive Anti-Itch Lotion	
Patient 5	35	Female	Hand	++: pramoxine 2% pet., Neosporin + Pain Relief Ointment	Benzocaine 5% pet., lidocaine 15% pet.	Neosporin + Pain Relief Ointment	
Patient 6	59	Female	Perianal	++/+++ pramoxine 2% pet., Preparation H ointment, Caladryl Clear Lotion	Benzocaine 5% pet., lidocaine 15% pet.	Preparation H ointment, Caladryl Clear Lotion	
Patient 7	36	Female	Diffuse	++: pramoxine 2% pet.	Benzocaine 5% pet., lidocaine 15% pet.	Unknown, likely antibiotic ointment per patient report	Pramoxine likely of past relevance
Patient 8	29	Female	Diffuse, facial	+: pramoxine 2% pet.	Benzocaine 5% pet., lidocaine 15% pet.	Unknown, likely antibiotic ointment per patient report	Pramoxine likely of past relevance

aq., aqueous; NR, not reported; pet., petrolatum.

reading showed mild (+) reactions to Nikzon and Prax Lotion, as well as his Sarna, Preparation H cream, and hemorrhoid pads. Other ingredients in these products were negative.

Patient 3

A 33-year-old man presented with a 9-month history of lower leg/dorsal foot dermatitis (Fig. 2A). He had tried several treatments including Walgreens Calamine Plus Spray, which declared pramoxine. Day 5

reading showed a strong (++) reaction to pramoxine hydrochloride (2% pet.; Chemotechnique Diagnostics, Vellinge, Sweden) and a mild (+) reaction to his calamine spray (Figs. 2B, C). Other ingredients in the calamine spray were negative.

Patient 4

A 63-year-old man presented with a 10-year history of diffuse body dermatitis. He had tried several treatments including Sarna Sensitive



Figure 1. Patient 1's (A) hand and fingertip dermatitis. Final patch test results showing strong (+++) reactions to (B) Prax Lotion at 48 hours, (C) Nikzon at 48 hours, and her (D) Neosporin ointment at 96 hours.

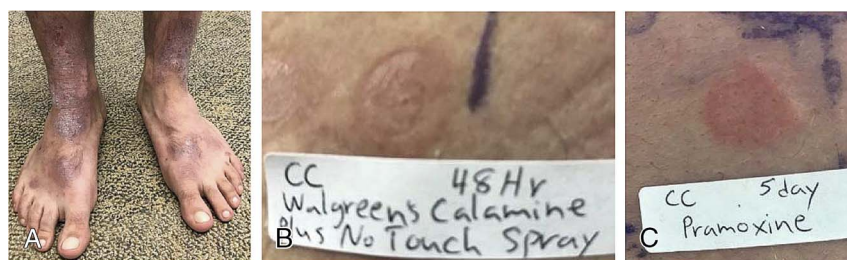


Figure 2. Patient 3: (A) lower leg/foot dermatitis. Day 3 patch test results showing a mild (+) reaction to his (B) calamine spray. Day 5 results showed a strong (++) reaction to pramoxine (C) and the calamine spray (not pictured).



Figure 3. Patient 4's day 5 patch test results showing strong (++) reactions to (A) pramoxine and (B) Sarna Sensitive Anti-Itch Lotion (48-hour reading; was added when patient brought product to 48-hour reading).

Anti-Itch Lotion; this notably worsened his rash. Day 5 reading showed strong (++) reactions to pramoxine and his Sarna Sensitive Anti-Itch Lotion, which was added at the 48-hour reading (Fig. 3).

Patient 5

A 35-year-old woman presented for a 10-year history of hand dermatitis (Fig. 4A). She tried several treatments including Neosporin + Pain Relief Ointment; this consistently worsened her rash. Day 5 reading showed strong (++) reactions to pramoxine and her Neosporin ointment, which contained pramoxine (Figs. 4B, C).

Patient 6

A 59-year-old woman presented for a 7-month history of perianal dermatitis. She had used Preparation H ointment on her hemorrhoids and subsequently developed a pruritic, vesicular rash. She also acknowledged a previous, vesicular rash after using Caladryl

Clear lotion elsewhere. Day 7 reading showed strong (++) reactions to pramoxine and her Caladryl and Preparation H, both of which contained pramoxine (Fig. 5).

Patients 7 and 8

These patients both had used triple antibiotic ointment on their dermatitis in the past but no longer had the product, so definite clinical relevance could not be established.

Summary of Cases

The 6 reported cases and our additional 8 cases are summarized in Table 4. Patients were aged 29 to 76 years (average age, 49.9 years). Five were male, and 7 were female (sex not reported, $n = 2$). Common sites of dermatitis were scattered/diffuse ($n = 4$), anogenital area ($n = 4$), hands ($n = 2$), at the site of existing wounds ($n = 2$).



Figure 4. Patient 5's (A) hand dermatitis. Day 5 patch test results showing strong (++) reactions to (B) pramoxine and (C) Neosporin ointment containing pramoxine.



Figure 5. Patient 6's day 7 patch test results showing a strong (++) reaction to (A) pramoxine and very strong (+++) reactions to (B) Preparation H Cream and Caladryl Clear Lotion, both containing pramoxine.

Responsible topical products included preparations for treatment of itch ($n = 6$), infections/wounds ($n = 5$), and hemorrhoids/anogenital irritation ($n = 5$). Twelve of 14 patients were tested to at least 1 amide and at least 1 ester topical LA, and only 1 of these 12 patients was positive to another topical anesthetic.

DISCUSSION

Unlike allergy to other topical anesthetics (eg, benzocaine, tetracaine), contact dermatitis to pramoxine is poorly reported in the literature. Given the frequency and relevance of strong pramoxine patch test reactions we have seen with only intermittent testing, we believe that it is an underrecognized allergen. We recommend regular patch testing to pramoxine in patients who have used any over-the-counter treatments of their rash, particularly those who affirm use of anti-itch, pain-relief, or antibiotic topicals either currently or in the past. Pramoxine-containing products are often used by patients to treat existing wounds or rash and thus may be an important cause of exacerbation of existing skin conditions. Pramoxine does not seem to cross-react with amide or ester topical anesthetics. Further studies are needed not only to assess frequency in consecutively tested patients but also to further delineate cross-reactivity.

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