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Case Series

Allergic Contact Dermatitis and Autoeczematization to Proctosedyl® Cream and Proctomyxin® Cream

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Keywords

Allergic contact dermatitis · Proctosedyl® cream · Proctomyxin® cream · Hemorrhoids · Patch test · Cross-reactivity

Abstract

Proctosedyl® and Proctomyxin® are two commonly prescribed hemorrhoid therapies. Their topical application to the perianal region may be complicated by a local allergic contact dermatitis and subsequent autoeczematization reaction. We present three cases of an autoeczematization (ID) reaction to varying topical allergens found in Proctosedyl®/Proctomyxin®. It is our recommendation that physician and patient education, avoidance of allergens (or cross-reactants), and appropriate choice of topical corticosteroid is important in preventing and avoiding flares.

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Introduction

Proctosedyl® cream (Sanofi-Aventis, Paris, France) and Proctomyxin® cream (Novartis, Basel, Switzerland) are common medications used to treat hemorrhoids. Framycetin, hydrocortisone, and dibucaine (cinchocaine) are 3 active ingredients in these creams. These ingredients are common in over-the-counter (OTC) medications and are potential allergens [1].

We present 3 cases of allergic contact dermatitis (ACD) in males who used Proctosedyl® cream and Proctomyxin® cream to treat their hemorrhoids; 2 of these men experienced an autoeczematization.

Case Reports

Case 1

A 72-year-old man presented to the emergency department with a very pruritic, tender, erythematous eczematous dermatitis that started in the perianal area and then became more widespread. A diagnosis of ACD in his perianal region likely due to Proctosedyl®, a cream to treat his hemorrhoids, was made. He had previously used Lamisil® cream (Novartis), Benadryl® cream (Johnson & Johnson, New Brunswick, NJ, USA), and 2 hydrocortisone preparations (Imacort® [Spirig, Egerkingen, Switzerland] and Cortoderm® [Pharmacare Ltd., Port Elizabeth, South Africa]).

He was subsequently patch tested with readings completed at 48 and 96 h. His results were strongly positive (3+) for gentamicin sulfate 20% in pet, kanamycin sulfate 20% in pet, framycetin sulfate 10% in pet, rosin 20% in pet, tixocortol-21-pivalate 1% in pet, and hydrocortisone 1% in pet. Specific results at 96 h (true allergens) are shown in Table 1 (medication is listed in Table 2). Our patient was advised about all his contact allergies and potential cross-reactions. He was prescribed Betaderm® 0.1% ointment (a safe group 3 [D1] steroid) for potential future reactions and Protopic cream® (Astella/Fujisawa, Tokyo, Japan) for facial eruptions.

Case 2

A 27-year-old man presented with severe ACD in the perianal region followed by a widespread flare of his eczema (autoeczematization) to Proctomyxin® cream. He used Proctomyxin® cream, Proctozone® (Rising, Allendale, NJ, USA), Anusol HC® (Salix, Raleigh, NC, USA), Polysporin® Complete (Johnson & Johnson), and Proctofoam® cream (Meda, Somerset, NJ, USA) to treat his hemorrhoids (see Table 2 for ingredients). He was started on 50 mg of oral prednisone and weaned down over 3 weeks. He was also given topical betamethasone 0.1% ointment.

He was subsequently patch tested, and results were read at 48 and 120 h; the results are summarized in Table 1. He was strongly reactive (3+) to neomycin sulfate 20% in pet, gentamicin sulfate 20% in pet, kanamycin sulfate 10% in pet, framycetin sulfate 10% in pet, dibucaine HCl 5% in pet, lanolin alcohol (Amerchol L-101) 50% in pet, carba mix 3% in pet, Proctozone® cream, Anusol HC® cream, chlorhexidine digluconate 0.5% aq, and Proctomyxin® cream. He was educated regarding which safe skin products he could use (Lipikar®

balm [F. Hoffmann-La Roche AG, Basel, Switzerland], Dove® for sensitive skin [Unilever, UK]). He was advised about all his contact allergies, their sources and cross-reactions.

Case 3

A 44-year-old man presented to the emergency room with a history of a pruritic, spreading perianal eczematous dermatitis, which developed 2 days after commencing Proctosedyl® cream treatment for his hemorrhoids. He also started 1% hydrocortisone cream. He developed an autoeczematization reaction in his body folds (axilla, antecubital fossa, and ankles); this reaction persisted for a few weeks. His pruritus was controlled with Claritin® (Schering-Plough, Kenilworth, NJ, USA) and Reactine® (Johnson & Johnson). Past history revealed the use of Kenacomb® cream (GlaxoSmithKline, Brentford, London, UK) for an axillary rash 12 years before, which resulted in a similar clinical picture of ACD. He was given Atarax® (GlaxoSmithKline) (hydroxyzine) to treat his Kenacomb cream-induced ACD. His ACD worsened and became generalized.

Two rounds of patch testing were completed and results were read at 48 h and the 120-h mark. Results are summarized in the corresponding Table 1 and Figure 1. He was positive for all tested cross-reacting aminoglycosides (neomycin sulfate, gentamycin sulfate, kanamycin sulfate, and framycetin sulfate) as well as the co-reacting bacitracin. He was also strongly positive for dibucaine (chichocaine HCl 5% in pet), tixocortol-21-pivalate 1% in pet (screens for group A [now group I] hydrocortisone allergy), ethylenediamine dihydrochloride 1% in pet, thiuram mix 1% in pet (rubber), fragrance mix 8% in pet, and triamcinolone acetonide and its screener for group B (now group II) corticosteroid allergy budesonide 0.1% in pet. Kenacomb® contains ethylenediamine, triamcinolone acetonide 1% in pet, and neomycin, to all of which the patient had a very strong reaction, in addition to the whole Kenacomb® cream preparation. Ethylenediamine dihydrochloride, an ingredient used as a stabilizer in Kenacomb® cream, cross-reacts with hydroxyzine (Atarax® and Reactine®) [2]. This caused a systemic contact dermatitis reaction when the patient took hydroxyzine for his original ACD to Proctosedyl® cream. Proctosedyl® cream contains hydrocortisone acetate and dibucaine HCl. Again, the patient had a strong reaction to both ingredients plus the whole preparation.

In all 3 cases, the patients were tested in accordance with the North American Contact Dermatitis Group (NACDG) [1] protocol and the NACDG standard screening series using Finn Chambers (allergEAZE; SmartPractice, Phoenix, AZ, USA) and Scanpor tape (Norgesplaster Alpharma, Vennesla, Norway), as well as the other series, which can be seen in Table 1.

Discussion

It is estimated that ACD affects 15–20% of the general population at some point [3]. ACD risk factors are divided into acquired and inherited categories. Acquired risk factors include stasis dermatitis, polysensitization, and irritant contact dermatitis. Inherited risk factors include genetic mutations (Table 3), young age (due to increased immune function), female gender, and possibly lighter skin color due to decreased barrier function [3].

Clinical Presentation

ACD classically presents acutely as a papulovesicular, edematous, erythematous spreading eruption. Scaling may occur in subacute lesions and thickened plaques; lichenification or fissuring may be seen in chronic cases [4]. As in our cases, sensitization to multiple allergens, or polysensitization, can occur. A detailed history, including the points in Table 4, is important to help elucidate allergen sources. Polysensitization is subcategorized into co-sensitization (co-reactivity) and cross-sensitization. Co-sensitization is when multiple sensitizations occur to immunologically distinct chemicals at the same time. Cross-sensitization is when the 2 different antigens appear similar to the immune system. As mentioned, autoeczematization is a full-body ACD flare from a topical agent, whereas a systemic reaction appears the same but occurs secondary to a parenteral exposure.

Pathophysiology

ACD is a classic T-cell-mediated hypersensitivity to exogenous agents. Initially, low-molecular-weight (<500 Da) chemicals (haptens), which are nonimmunogenic, penetrate the stratum corneum and covalently bind to amino acid side chains [5]. Next, the sensitization phase occurs when the hapten-protein complex is engulfed by Langerhans cells and drained to the regional lymph node. Clonal expansion occurs and T cells circulate the body before the elicitation phase occurs [6]. The elicitation phase commences when a T-cell- (primarily CD8+ Tc1 cells) mediated inflammatory response ensues as a consequence of being re-exposed to a cross-reactive or previously sensitized agent [7].

Treatment

The mainstay of ACD treatment is allergen identification through patch testing and avoidance, which needs to be clearly conveyed to the patient. Short-term management of acute flares may require the use of topical corticosteroids. The use of betamethasone valerate (group D1) or desoximetasone (group C) is recommended, as they are the least allergenic corticosteroids. Oral prednisone is added in more severe cases. Calcineurin inhibitors (tacrolimus or pimecrolimus) in place of corticosteroids are acceptable, especially in cases involving the face or eyelids. In rare systemic cases, immunosuppressive agents have been successfully used (i.e., unavoidable airborne allergens like dust).

Proctosedyl® cream (specifically its constituent dibucaine) as a vehicle for ACD allergens was first described in a case report published by Lee in 1998 [8]. A second case report by Kearney and Fewings [8] attributed ACD to dibucaine (aka cinchocaine) in 2001; but these remain 2 isolated case reports demonstrating a direct link. At times, lidocaine and dibucaine can cross-react. However, the NACDG patch test results from 2011 to 2012 demonstrate that 9.1% (n = 384) of patch-tested patients had a definitive ACD reaction to neomycin [9]; this substance commonly cross-reacts with framycetin (in our patients' hemorrhoid creams), since both are aminoglycoside topical antibiotics.

Based on the history and patch testing results demonstrated by our cases, the following was surmised. These patients were sensitized to multiple distinct components. Their exposure to Proctosedyl® cream and Proctomyxin cream® caused a range of reactions along the ACD spectrum. The re-exposure to similar agents (cases 2 and 3) consequently created a widespread autoeczematization that required oral prednisone. It was concluded that Proctosedyl®

cream and Proctomyxin® cream were responsible in all 3 cases of ACD. One case had systemic contact dermatitis from a parental exposure to hydroxyzine and Reactine®.

Factors that contribute to sensitization include warm, moist, intertriginous areas that are fissured, such as the perianal region. Other high-risk sites are venous stasis dermatitis of the lower legs, otitis externa, perivulvar areas, eyelids, and legs.

Conclusions

These 3 ACD cases secondary to hemorrhoid treatment demonstrate several unique features. This report is an example of multiple patients with polysensitization to multiple unrelated allergies in hemorrhoid preparations (Proctosedyl® cream, Proctomyxin® cream, Anusol HC®, and Proctozone®). Second, it demonstrates the broad possible cross-reactivity to other medications which physicians and patients must be diligent to avoid. Finally, 2 of these cases showed autoeczematization, and 1 case is an example of a systemic reaction.

Key Points

- ACD requires sensitization prior to elicitation of clinical findings.
- When ACD findings are present, all offending agents should be stopped in order to prevent worsening of existing rashes or an autoeczematization reaction.
- When establishing a diagnosis, an accurate detailed history and patch testing helps determine the cause of ACD.
- The management of allergic contact includes patient education, allergen avoidance, appropriate topical steroids (betamethasone) that are less allergic, and follow-up.
- Also, avoiding multiple OTC products is necessary, such as wet wipes, OTC hydrocortisone cream, etc.
- Safe products include gentle bar soap (Aveno Bar®), plain Vaseline, and Betaderm ointment if perianal pruritis develops.

Statement of Ethics

All patients in this study have consented to the use of nonidentifiable personal information for the purposes of this publication.

Disclosure Statement

No author involved in this study has any conflicts of interest to disclose.

References

1 Pratt MD, Belsito DV, DeLeo VA, Fowler JF Jr, Fransway AF, Maibach HI et al. North American Contact Dermatitis Group patch-test results, 2001-2002 study period. Dermatitis. 2004 Dec;15(4):176–83.
2 Lew BL, Haw CR, Lee MH. Cutaneous drug eruption from cetirizine and hydroxyzine. J Am Acad Dermatol. 2004 Jun;50(6):953–6.
3 Peiser M, Tralau T, Heidler J, Api AM, Arts JH, Basketter DA et al. Allergic contact dermatitis: epidemiology, molecular mechanisms, in vitro methods and regulatory aspects. Current knowledge assembled at an international workshop at BfR, Germany. Cell Mol Life Sci. 2012 Mar;69(5):763–81.
4 Bolognia J, Schaffer J, Duncan K, Ko C. Dermatology Essentials. China: Elsevier; 2014.
5 Divkovic M, Pease CK, Gerberick GF, Basketter DA. Hapten-protein binding: from theory to practical application in the in vitro prediction of skin sensitization. Contact Dermat. 2005 Oct;53(4):189–200.
6 Vocanson M, Hennino A, Rozières A, Poyet G, Nicolas JF. Effector and regulatory mechanisms in allergic contact dermatitis. Allergy. 2009 Dec;64(12):1699–714.
7 Vocanson M, Hennino A, Cluzel-Tailhardat M, Saint-Mezard P, Benetiere J, Chavagnac C, et al. CD8+ T cells are effector cells of contact dermatitis to common skin allergens in mice. J Invest Dermatol. 2006 Apr;126(4):815–20.
8 Kearney CR, Fewings J. Allergic contact dermatitis to cinchocaine. Australas J Dermatol. 2001 May;42(2):118–9.
9 Warshaw EM, Maibach HI, Taylor JS, Sasseville D, DeKoven JG, Zirwas MJ et al. North American Contact Dermatitis Group patch test results: 2011-2012. Dermatitis. 2015 Jan-Feb;26(1):49–59.

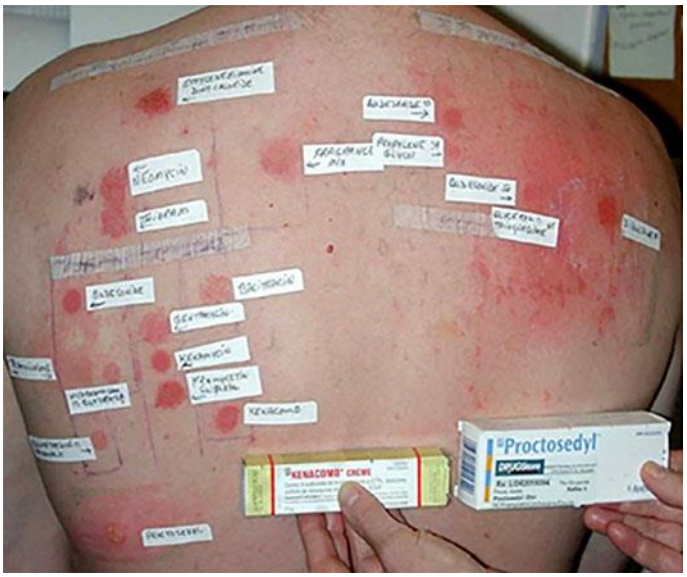

Fig. 1. Case 3. Patch test results at 120 h. Note the individual eczematous patches present at 120 h despite background erythema which persisted 72 h after the removal of his patches.

Table 1. Summary of the patch test results for all 3 patients

Compound	Case 1	Case 2	Case 3
Aminoglycosides			
Neomycin sulfate 20% in pet	–	3+	3+
Gentamicin sulfate 20% in pet	3+	3+	3+
Kanamycin sulfate 10% in pet	3+	3+	3+
Framycetin[a] sulfate 10% in pet	3+	3+	3+
Bacitracin 20% in pet			3+
Other tested compounds			
Rosin[b] (Colophonium) 20% in pet	2+	1+	–
Tixocortol-21-pivalate[c] 1% in pet	3+	–	3+
Carba mix 3% in pet	–	3+	–
Diphenyl guanidine[d] 1% in pet	–	1+	–
Lanolin alcohol (Amerchol L-101) 50% in pet	–	3+	–
Dibucaine or cinchocaine HCl 5% in pet	–	3+	3+
Proctozone® cream	–	3+	–
Anusol HC® cream (Salix, Raleigh, NC, USA)	–	3+	–
Benzophenone-4[e] (Sulisobenzone)	–	2+	–
Chlorhexidine[f] digluconate 0.5% aq	–	3+	–
Hydrocortisone cream 1% (1)	3+	–	3+
Proctosedyl cream	3+	–	3+
Benadryl cream (1)	3+	–	–
Proctomyxin® cream (2)	–	3+	–
Kenacomb cream	–	–	3+
Thiuram mix 1% in pet	–	–	3+
Ethylenediamine dihydrochloride 1% in pet	–	–	3+
Fragrance I 8% in pet	–	–	3+
Triamcinolone acetonide 1% in pet	–	–	3+
Alclometasone-17,21-diproprionate 1% in pet	–	–	2+
Budesonide 0.1% in pet	–	–	3+

All results were recorded at 96–120 h as per the NACDG guidelines. Results at 48 h are excluded for simplicity and accuracy. [a] Framycetin: found in Proctosedyl®. [b] Rosin: sap/pitch from pine trees used in Band-Aids. [c] Tixocortol-21-pivalate: screen for hydrocortisone allergy. [d] Diphenyl guanidine: part of carba, a rubber accelerator. [e] Benzophenone (sulisobenzone): found in sunscreens and shampoos. [f] Chlorhexidine: antibacterial agent found in cleansers, toothpaste, and shampoos.

Table 2. Topical medications used by our patients and their ingredients

Medication	Ingredient	Ingredient
Proctosedyl® cream (in 1 g)	Hydrocortisone BP 5 mg (0.5%) Cinchocaine hydrochloride BP 5 mg (0.5%)	Esculin 10 mg (1%) Anhydrous lanolin Framycetin sulfate BP 10 mg
Proctomyxin® cream (in 1 g)	Hydrocortisone 5 mg (0.5%) Framycetin sulfate 10 mg Anhydrous lanolin	Cinchocaine hydrochloride 5 mg (0.5%) Esculin 10 mg (1%)
Proctozone® (in 1 g)	Hydrocortisone (as acetate) 5 mg Framycetin sulfate 10 mg Cinchocaine hydrochloride 5 mg Esculin 10 mg	Lanolin Light mineral oil Petrolatum
Anusol HC® (in 1 g)	Zinc sulfate monohydrate 0.5% Calcium phosphate (dibasic) Methylparaben Mineral oil	Oleth-2 Petrolatum Propyl paraben
Polysporin® (in 1 g)	10,000 units Polymyxin B (as sulfate) 500 units bacitracin zinc Butylated hydroxytoluene Cocoa butter	Vitamin E Sodium pyruvate Olive oil, petrolatum Cotton seed oil
Proctofoam® (in 375 mg)	1% hydrocortisone acetate (3.75 mg/dose) 1% pramoxine hydrochloride (3.75 mg/dose) Cetyl alcohol Emulsifying wax Isobutane	Water Triethanolamine Steareth-10 Propylparaben Propylene glycol Propane Methylparaben
Kenacomb®[a]	Nystatin Gramicidin Ethylenediamine	Neomycin Triamcinolone acetonide
Atarax®	Hydroxyzine Hydrocholoride (10 mg) Wax mixture	Soybean oil Lecithin

[a] Bristol Myers Squibb could not directly comment on the ingredients in Kenacomb as it is discontinued.

Table 3. Genetic risk factors for ACD and their effects

Genetic mutation	Effect
Metabolism and activation of NATs	*Patients with ACD tend to have NATs with higher enzymatic activity*
Homogeneous deletion of glutathione *S*-transferases (GSTs) M1 and T1	*Increased sensitization against preservative thimerosal*
Cytokine polymorphisms	*Change immunologic response*
Promoter of TNF-α at position 308	*Higher susceptibility to chromate in cement workers*
Homozygous allele IL-16^{-295C}	*Higher frequency in polysensitized individuals*

ACD, allergic contact dermatitis; NAT, *N*-acetyltransferase.

Table 4. Important history points

Demographics and occupational history	Age Religion Job title Regular exposures Occasional exposures Time at current job	Gender Ethnicity Social aspects (marital status) Job description Employment location Previous occupation
Family medical history	Genetic factors	Predisposition
Past medical history	Drug allergies Medications	Concomitant diseases Surgeries
Dermatitis-specific history	Onset Temporal association (waxing/waning)	Location Treatment