Contact Allergy to Topical Medicaments, Part 2: Steroids, Immunomodulators, and Anesthetics, Oh My!

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PRACTICE **POINTS**

- Allergic contact dermatitis (ACD) should be suspected in patients with persistent or worsening dermatitis after use of topical medications.
- Cross-reactions commonly occur between structurally similar compounds and occasionally between molecules from different drug classes.
- Some cases of topical medicament ACD remain elusive after patch testing, particularly drugs with potent immunomodulating effects.

Topical drugs are used to treat a variety of cutaneous and noncutaneous conditions. Direct application to the skin can result in adverse cutaneous effects, including allergic contact dermatitis (ACD). In part 2 of this series on topical medicament ACD, we focus on corticosteroids, immunomodulators, and anesthetics.

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In the first part of this 2-part series (*Cutis.* 2021; 108:271-275), we discussed topical medicament allergic contact dermatitis (ACD) from acne and rosacea medications, antimicrobials, antihistamines, and topical pain preparations. In part 2 of this series, we focus on topical corticosteroids, immunomodulators, and anesthetics.

Corticosteroids

Given their anti-inflammatory and immune-modulating effects, topical corticosteroids are utilized for the treatment of contact dermatitis and yet also are frequent culprits of ACD. The North American Contact Dermatitis Group (NACDG) demonstrated a 4% frequency of positive patch tests to at least one corticosteroid from 2007 to 2014; the relevant allergens were tixocortol pivalate (TP)(2.3%), budesonide (0.9%), hydrocortisone-17-butyrate (0.4%), clobetasol-17-propionate (0.3%), and desoximetasone (0.2%).[1] Corticosteroid contact allergy can be difficult to recognize and may present as a flare of the underlying condition being treated. Clinically, these rashes may demonstrate an edge effect, characterized by pronounced dermatitis adjacent to and surrounding the treatment area due to concentrated anti-inflammatory effects in the center.

Traditionally, corticosteroids are divided into 4 basic structural groups—classes A, B, C, and D—based on the Coopman et al[2] classification (Table). The class D corticosteroids were further subdivided into classes D1, defined by C16-methyl substitution and halogenation of the B ring, and D2, which lacks the aforementioned substitutions.[4] However, more recently Baeck et al[5] simplified this classification into 3 main groups of steroids based on molecular modeling in combination with patch test results. Group 1 combines the nonmethylated and (mostly) nonhalogenated

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Ms. Ng and Dr. Reeder report no conflict of interest. Dr. Atwater is Immediate Past President of the American Contact Dermatitis Society (ACDS) and is an employee of Eli Lilly and Company.

This article is the second of a 2-part series. Part 1 appeared in November 2021.

The eTable is available in the Appendix online at www.mdedge.com/dermatology.

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Class A–D Corticosteroid Classification System[2-4]

Class	Type	Structural characteristics	Cross-reaction patterns	Corticosteroids
A	Hydrocortisone	No D-ring substitution, except a C21 short-chain ester or C21 thioester	Group A, group D2	Cloprednol, cortisone, cortisone acetate, fludrocortisone, hydrocortisone, hydrocortisone acetate, methylprednisolone acetate, prednisolone, prednisolone acetate, tixocortol pivalate
B	Triamcinolone acetonide	C16, C17 *cis* ketal or diol structure	Group B, group D2	Amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, halcinonide, triamcinolone acetonide, triamcinolone alcohol
C	Betamethasone	C16-methyl substitution	No significant cross-reaction patterns	Betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone
D1	Betamethasone dipropionate	C17/C21 long-chain ester +/− C16-methyl substitution, C16-methyl substitution, B-ring halogenation	No significant cross-reaction patterns	Alclometasone dipropionate, betamethasone valerate, betamethasone dipropionate, clobetasol-17-propionate, clobetasone butyrate
D2	Methylprednisolone aceponate	C17/C21 long-chain ester +/− C16-methyl substitution	Group D2; group A; budesonide, (S)-isomer	Hydrocortisone-17-butyrate, hydrocortisone valerate

class A and D2 molecules plus budesonide; group 2 accounts for some halogenated class B molecules with the C16, C17 *cis* ketal or diol structure; and group 3 includes halogenated and C16-methylated molecules from classes C and D1.[4] For the purposes of this review, discussion of classes A through D refers to the Coopman et al[2] classification, and groups 1 through 3 refers to Baeck et al.[5]

Tixocortol pivalate is used as a surrogate marker for hydrocortisone allergy and other class A corticosteroids and is part of the group 1 steroid classification. Interestingly, patients with TP-positive patch tests may not exhibit signs or symptoms of ACD from the use of hydrocortisone products. Repeat open application testing (ROAT) or provocative use testing may elicit a positive response in these patients, especially with the use of hydrocortisone cream (vs ointment), likely due to greater transepidermal penetration.[6] There is little consensus on the optimal concentration of TP for patch testing. Although TP 1% often is recommended, studies have shown mixed findings of notable differences between high (1% petrolatum) and low (0.1% petrolatum) concentrations of TP.[7,8]

Budesonide also is part of group 1 and is a marker for contact allergy to class B corticosteroids, such as triamcinolone and fluocinonide. Cross-reactions between budesonide and other corticosteroids traditionally classified as group B may be explained by structural similarities, whereas cross-reactions with certain class D corticosteroids, such as hydrocortisone-17-butyrate, may be better explained by the diastereomer composition of budesonide.[9,10] In a European study, budesonide 0.01% and TP 0.1% included in the European Baseline Series detected 85% (23/27) of cases of corticosteroid allergies.[11] Use of inhaled budesonide can provoke recall dermatitis and therefore should be avoided in allergic patients.[12]

Testing for ACD to topical steroids is complex, as the potent anti-inflammatory properties of these medications can complicate results. Selecting the appropriate test, vehicle, and concentration can help avoid false negatives. Although intradermal testing previously was thought to be superior to patch testing in detecting topical corticosteroid contact allergy, newer data have demonstrated strong concordance between the two methods.[13,14] The risk for skin atrophy, particularly with the use of suspensions, limits the use of intradermal testing.[14] An ethanol vehicle is recommended for patch testing, except when testing with TP or budesonide when petrolatum provides greater corticosteroid stability.[14-16] An irritant pattern or a rim effect on patch testing often is considered positive when testing corticosteroids, as the effect of the steroid itself can diminish a positive reaction. As a result, 0.1% dilutions sometimes are favored over 1% test concentrations.[14,15,17] Late readings (>7 days) may be necessary to detect positive reactions in both adults and children.[18,19]

The authors (M.R., A.R.A.) find these varied classifications of steroids daunting (and somewhat confusing!). In general, when ACD to topical steroids is suspected, in

addition to standard patch testing with a corticosteroid series, ROAT of the suspected steroid may be necessary, as the rules of steroid classification may not be reproducible in the real world. For patients with only corticosteroid allergy, calcineurin inhibitors are a safe alternative.

Immunomodulators

Calcipotriol is a vitamin D analogue commonly used to treat psoriasis. Although it is a well-known irritant, ACD to topical calcipotriol rarely has been reported.[20-23] Topical calcipotriol does not seem to cross-react with other vitamin D analogues, including tacalcitol and calcitriol.[21,24] Based on the literature and the nonirritant reactive thresholds described by Fullerton et al,[25] recommended patch test concentrations of calcipotriol in isopropanol are 2 to 10 µg/mL. Given its immunomodulating effects, calcipotriol may suppress contact hypersensitization from other allergens, similar to the effects seen with UV radiation.[26]

Calcineurin inhibitors act on the nuclear factor of activated T cells signaling pathway, resulting in downstream suppression of proinflammatory cytokines. Contact allergy to these topical medications is rare and mainly has involved pimecrolimus.[27-30] In one case, a patient with a previously documented topical tacrolimus contact allergy demonstrated cross-reactivity with pimecrolimus on a double-blinded, right-vs-left ROAT, as well as by patch testing with pimecrolimus cream 1%, which was only weakly positive (+).[27] Patch test concentrations of 2.5% or higher may be required to elicit positive reactions to tacrolimus, as shown in one case where this was attributed to high molecular weight and poor extrafacial skin absorption of tacrolimus.[30] In an unusual case, a patient reacted positively to patch testing and ROAT using pimecrolimus cream 1% but not pimecrolimus 1% to 5% in petrolatum or alcohol nor the individual excipients, illustrating the importance of testing with both active and inactive ingredients.[29]

Anesthetics

Local anesthetics can be separated into 2 main groups—amides and esters—based on their chemical structures. From 2001 to 2004, the NACDG patch tested 10,061 patients and found 344 (3.4%) with a positive reaction to at least one topical anesthetic.[31] We will discuss some of the allergic cutaneous reactions associated with topical benzocaine (an ester) and lidocaine and prilocaine (amides).

According to the NACDG, the estimated prevalence of topical benzocaine allergy from 2001 to 2018 was roughly 3%.[32] Allergic contact dermatitis has been reported in patients who used topical benzocaine to treat localized pain disorders, including herpes zoster and dental pain.[33,34] Benzocaine may be used in the anogenital region in the form of antihemorrhoidal creams and in condoms and is a considerably more common allergen in those with anogenital dermatitis compared to those without.[35-38] Although cross-reactions within the same anesthetic group are common, clinicians also should be aware of the potential for concomitant sensitivity between unrelated local anesthetics.[39-41]

From 2001 to 2018, the prevalence of ACD to topical lidocaine was estimated to be 7.9%, according to the NACDG.[32] A topical anesthetic containing both lidocaine and prilocaine often is used preprocedurally and can be a source of ACD. Interestingly, several cases of ACD to combination lidocaine/prilocaine cream demonstrated positive patch tests to prilocaine but not lidocaine, despite their structural similarities.[42-44] One case report described simultaneous positive reactions to both prilocaine 5% and lidocaine 1%.[45]

There are a few key points to consider when working up contact allergy to local anesthetics. Patients who develop positive patch test reactions to a local anesthetic should undergo further testing to better understand alternatives and future use. As previously mentioned, ACD to one anesthetic does not necessarily preclude the use of other related anesthetics. Intradermal testing may help differentiate immediate and delayed-type allergic reactions to local anesthetics and should therefore follow positive patch tests.[46] Importantly, a delayed reading (ie, after day 6 or 7) also should be performed as part of intradermal testing. Patients with positive patch tests but negative intradermal test results may be able to tolerate systemic anesthetic use.[47]

Patch Testing for Potential Medicament ACD

In this article, we touched on several topical medications that have nuanced patch testing specifications given their immunomodulating effects. A simplified outline of recommended patch test concentrations is provided in the eTable, and we encourage you to revisit these useful resources as needed. In many cases, referral to a specialized patch test clinic may be necessary. Although they are not reviewed in this article, always consider inactive ingredients such as preservatives, softening agents, and emulsifiers in the setting of medicament dermatitis, as they also may be culprits of ACD.

Final Interpretation

In this 2-part series, we covered ACD to several common topical drugs with a focus on active ingredients as the source of allergy, and yet this is just the tip of the iceberg. Topical medicaments are prevalent in the field of dermatology, and associated cases of ACD have been reported proportionately. Consider ACD when topical medication efficacy plateaus, triggers new-onset dermatitis, or seems to exacerbate an underlying dermatitis.

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APPENDIX

eTABLE. Recommended Patch Test Concentrations

Topical medicament	Test concentration and vehicle[a]
Benzocaine	5% petrolatum
Budesonide	0.1% petrolatum
Calcipotriol	2 µg/mL alcohol, 2–10 µg/mL isopropanol
Calcitriol	0.0002% alcohol
Clobetasol-17-propionate	0.5% petrolatum, 1% alcohol
Desoximetasone	1% petrolatum, 1% epi, 1% alcohol
Hydrocortisone-17-butyrate	1% alcohol, 1% petrolatum
Lidocaine	15% petrolatum, 5% petrolatum
Pimecrolimus	1% vehicle as provided by manufacturer[27,48]
Prilocaine hydrochloride	5% petrolatum, 2% water
Tacalcitol	2 µg/mL alcohol
Tacrolimus	2.5% petrolatum
Tixocortol pivalate	1% petrolatum, 0.1%–1% petrolatum

Abbreviation: epi, 45% alcohol/10% propylene glycol/45% isopropyl alcohol.

[a]Patch testing recommendations were derived from de Groot[49] unless otherwise indicated.