

Contact Allergy to Topical Medicaments, Part 1: A Double-edged Sword

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PRACTICE POINTS

- Allergic contact dermatitis should be suspected in patients with persistent or worsening dermatitis after use of topical medications.
- Prior sensitization is not always apparent, and cross-reactions may occur between structurally similar compounds.
- Although most medicaments can be patch tested as is, patch testing to the individual components may be necessary to identify the causative allergen.

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 this article, we review medicament ACD with a focus on acne and rosacea medications, antimicrobials, antihistamines, and topical pain preparations.

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Topical medications frequently are prescribed in dermatology and provide the advantages of direct skin penetration and targeted application while typically sparing patients from systemic effects. Adverse cutaneous effects include allergic contact dermatitis (ACD), irritant contact dermatitis (ICD), photosensitivity, urticaria, hyperpigmentation or hypopigmentation, atrophy, periorificial dermatitis, and acneform eruptions. Allergic contact dermatitis can develop from the active drug or vehicle components.

Patients with medicament ACD often present with symptoms of pruritus and dermatitis at the site of topical application. They may express concern that the medication is no longer working or seems to be making things

worse. Certain sites are more prone to developing medicament dermatitis, including the face, groin, and lower legs. Older adults may be more at risk. Other risk factors include pre-existing skin diseases such as stasis dermatitis, acne, psoriasis, atopic dermatitis, and genital dermatoses.¹ A review of 14,911 patch-tested patients from a single referral clinic revealed that 17.4% had iatrogenic contact dermatitis, with the most common culprits being topical antibiotics, antiseptics, and steroids.²

In this 2-part series, we will focus on the active drug as a source of ACD. Part 1 explores ACD associated with acne and rosacea medications, antimicrobials, antihistamines, and topical pain preparations.

Acne and Rosacea Medications

Retinoids—Topical retinoids are first-line acne treatments that help normalize skin keratinization. Irritant contact dermatitis from retinoids is a well-known and common side effect. Although far less common than ICD, ACD from topical retinoid use has been reported.^{3,4} Reactions to tretinoin are most frequently reported in the literature compared to adapalene gel⁵ and tazarotene foam, which have lower potential for sensitization.⁶ Allergic contact dermatitis also has been reported from retinyl palmitate^{7,8} in cosmetic creams and from occupational exposure in settings of industrial vitamin A production.⁹ Both ICD and ACD from topical retinoids can present with pruritus, erythema, and scaling. Given this clinical overlap between ACD and ICD, patch testing is crucial in differentiating the underlying etiology of the dermatitis.

Benzoyl Peroxide—Benzoyl peroxide (BP) is another popular topical acne treatment that targets *Cutibacterium acnes*, a bacterium often implicated in the pathogenesis of acne

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vulgaris. Similar to retinoids, ICD is more common than ACD. Several cases of ACD to BP have been reported.¹⁰⁻¹⁴ Occasionally, honey-colored crusting associated with ACD to BP can mimic impetigo.¹⁰ Aside from use of BP as an acne treatment, other potential exposures to BP include bleached flour¹³ and orthopedic bone cement. Occupations at risk for potential BP exposure include dental technicians¹⁵ and those working in plastic manufacturing.

Brimonidine—Brimonidine tartrate is a selective α_2 -adrenergic agonist initially used to treat open-angle glaucoma and also is used as a topical treatment for rosacea. Allergic reactions to brimonidine eye drops may present with periorbital hyperpigmentation and pruritic bullous lesions.¹⁶ Case reports of topical brimonidine ACD have demonstrated mixed patch test results, with positive patch tests to Mirvaso (Galderma) as is but negative patch tests to pure brimonidine tartrate 0.33%.^{17,18} Ringuet and Houle¹⁹ reported the first known positive patch test reaction to pure topical brimonidine, testing with brimonidine tartrate 1% in petrolatum.^{20,21} Clinicians should be attuned to ACD to topical brimonidine in patients previously treated for glaucoma, as prior use of ophthalmic preparations may result in sensitization.^{18,20}

Antimicrobials

Clindamycin—Clindamycin targets bacterial protein synthesis and is an effective adjunct in the treatment of acne. Despite its widespread and often long-term use, topical clindamycin is a weak sensitizer.²² To date, limited case reports on ACD to topical clindamycin exist.²³⁻²⁸ Rare clinical patterns of ACD to clindamycin include mimickers of irritant retinoid dermatitis, erythema multiforme, or pustular rosacea.^{25,26,29}

Metronidazole—Metronidazole is a bactericidal agent that disrupts nucleic acid synthesis with additional anti-inflammatory properties used in the treatment of rosacea. Allergic contact dermatitis to topical metronidazole has been reported.³⁰⁻³⁴ In 2006, Beutner et al³⁵ patch tested 215 patients using metronidazole gel 1%, which revealed no positive reactions to indicate contact sensitization. Similarly, Jappe et al³⁶ found no positive reactions to metronidazole 2% in petrolatum in their prospective analysis of 78 rosacea patients, further highlighting the exceptionally low incidence of ACD. Cross-reaction with isothiazolinone, which shares structurally similar properties to metronidazole, has been speculated.^{31,34} One patient developed an acute reaction to metronidazole gel 0.75% within 24 hours of application, suggesting that isothiazolinone may act as a sensitizer, though this relationship has not been proven.³¹

Neomycin—Neomycin blocks bacterial protein synthesis and is available in both prescription and over-the-counter (OTC) formulations. It commonly is used to treat and prevent superficial wound infections as an OTC antibiotic and also has otic, ophthalmologic, gastroenterologic, urologic, and peritoneal formulations. It also can be used in the dental and veterinary fields and

is present in some animal feeds and in trace amounts in some vaccines for humans. Neomycin is a common antibiotic contact allergen, and the most recently reported 2017-2018 North American Contact Dermatitis Group data cycle placed it at number 12 with 5.4% positivity.³⁷ Co-reactions with bacitracin can occur, substantially limiting OTC topical antibiotic options for allergic patients. A safe alternative for patients with neomycin (and bacitracin and polymyxin) contact allergy is prescription mupirocin.

Bacitracin—Bacitracin interferes with peptidoglycan and cell-wall synthesis to treat superficial cutaneous infections. Similar to neomycin, it also can be found in OTC antibiotic ointments as well as in antibacterial bandages. There are several case reports of patients with both type IV delayed hypersensitivity (contact dermatitis) and type I anaphylactic reactions to bacitracin³⁸⁻⁴⁰; patch testers should be aware of this rare association. Bacitracin was positive in 5.5% of patch tested patients in the 2017-2018 North American Contact Dermatitis Group data cycle,³⁷ and as with neomycin, bacitracin also is commonly patch tested in most screening patch test series.

Polymyxin—Polymyxin is a polypeptide topical antibiotic that is used to treat superficial wound infections and can be used in combination with neomycin and/or bacitracin. Historically, it is a less common antibiotic allergen; however, it is now frequently included in comprehensive patch test series, as the frequency of positive reactions seems to be increasing, probably due to polysensitization with neomycin and bacitracin.

Nystatin—Nystatin is an antifungal that binds to ergosterol and disrupts the cell wall. Cases exist of ACD to topical nystatin as well as systemic ACD from oral exposure, though both are quite rare. Authors have surmised that the overall low rates of ACD may be due to poor skin absorption of nystatin, which also can confound patch testing.^{41,42} For patients with suspected ACD to nystatin, repeat open application testing also can be performed to confirm allergy.

Imidazole Antifungals—Similar to nystatins, imidazole antifungals also work by disrupting the fungal cell wall. Imidazole antifungal preparations that have been reported to cause ACD include clotrimazole, miconazole, econazole, and isoconazole, and although cross-reactivity patterns have been described, they are not always reproducible with patch testing.⁴³ In one reported case, tioconazole found in an antifungal nail lacquer triggered ACD involving not only the fingers and toes but also the trunk.⁴⁴ Erythema multiforme-like reactions also have been described from topical use.⁴⁵ Commercial patch test preparations of the most common imidazole allergens do exist. Nonimidazole antifungals remain a safe option for allergic patients.

Antihistamines

Antihistamines, or H1-receptor antagonists, are marketed to be applied topically for relief of pruritus associated with allergic cutaneous reactions. Ironically, they are known

to be potent sensitizers themselves. There are 6 main chemical classes of antihistamines: phenothiazines, ethylenediamines, ethanolamines, alkylamines, piperazines, and piperidines. Goossens and Linsen⁴⁶ patch tested 12,460 patients from 1978 to 1997 and found the most positive reactions to promethazine (phenothiazine)(n=12), followed by diphenhydramine (ethanolamine)(n=8) and clemizole (benzimidazole)(n=6). The authors also noted cross-reactions between diphenhydramine derivatives and between promethazine and chlorpromazine.⁴⁶

Doxepin is a tricyclic antidepressant with antihistamine activity and is a well-documented sensitizer.⁴⁷⁻⁵² Taylor et al⁴⁷ evaluated 97 patients with chronic dermatoses, and patch testing revealed 17 (17.5%) positive reactions to doxepin cream, 13 (76.5%) of which were positive reactions to both the commercial cream and the active ingredient. Patch testing using doxepin dilution as low as 0.5% in petrolatum is sufficient to provoke a strong (+ +) allergic reaction.^{50,51} Early-onset ACD following the use of

doxepin cream suggests the possibility of prior sensitization, perhaps with a structurally similar phenothiazine drug.⁵¹ A keen suspicion for ACD in patients using doxepin cream for longer than the recommended duration can help make the diagnosis.^{49,52}

Topical Analgesics

Nonsteroidal Anti-inflammatory Drugs—Ketoprofen is one of the most frequent culprits of photoallergic contact dermatitis. Pruritic, papulovesicular, and bullous lesions typically develop acutely weeks after exposure. Prolonged photosensitivity is common and can last years after discontinuation of the nonsteroidal anti-inflammatory drug.⁵³ Cases of cross-reactions and co-sensitization to structurally similar substances have been reported, including to benzophenone-related chemicals in sunscreen and aldehyde groups in fragrance mix.^{53,54}

Diclofenac gel generally is well tolerated in the topical treatment of joint pain and inflammation. In the setting

Recommended Patch Testing Concentrations

Topical medicament	Test concentration and vehicle ^a
Retinoic acid (tretinoin)	0.005% alc, 0.05% pet and 0.01%–0.02% alc, 0.1% pet
Benzoyl peroxide	1% pet
Brimonidine	1% pet ²⁰
Clindamycin hydrochloride, clindamycin phosphate	1% water, 1% pet, 1%–20% water or pet
Metronidazole	2%–5% pet
Neomycin sulfate	20% pet
Bacitracin	5%–20% pet
Polymyxin B sulfate	3% pet
Nystatin	3% alc, 2% pet
Clotrimazole	1% MEK, 1% pet, 1% alc, 5% pet
Miconazole nitrate	2% alc, 1% alc, 2% pet
Econazole nitrate	2% alc, 1% alc, 1% pet
Isoconazole nitrate	1%–2% alc, 1% pet
Promethazine hydrochloride	1%–10% pet, 2% pet
Diphenhydramine hydrochloride	1% pet, 2% pet
Doxepin	0.5% and 1% pet, 5% pet
Ketoprofen	5% pet, 1% pet, 2.5%–5% pet
Diclofenac	2.5% pet, 2.5%–5% pet, 1% pet
Bufexamac	5% pet, 1% pet
Carprofen	10% pet, 5% pet
Cyclobenzaprine	1%–2% pet ⁶⁴
Amitriptyline	5% pet

Abbreviations: alc, alcohol; pet, petrolatum; MEK, methyl ethyl ketone.

^aPatch testing recommendations were derived from deGroot⁶⁵ unless otherwise indicated.

of ACD, patients typically present with dermatitis localized to the area of application.⁵⁵ Immediate cessation and avoidance of topical diclofenac are crucial components of management. Although systemic contact dermatitis has been reported with oral diclofenac use,⁵⁶ a recent report suggested that oral diclofenac may be well tolerated for some patients with topical ACD.⁵⁷

Publications on bufexamac-induced ACD mainly consist of international reports, as this medication has been discontinued in the United States. Bufexamac is a highly sensitizing agent that can lead to severe polymorphic eruptions requiring treatment with prednisolone and even hospitalization.⁵⁸ In one Australian case report, a mother developed an edematous, erythematous, papulovesicular eruption on the breast while breastfeeding her baby, who was being treated with bufexamac cream 5% for infantile eczema.⁵⁹ Carprofen-induced photoallergic contact dermatitis is associated with occupational exposure in pharmaceutical workers.^{60,61} A few case reports on other nonsteroidal anti-inflammatory drugs, including etofenamate and aceclofenac, have been published.^{62,63}

Compounded Medications—Compounded topical analgesics, which help to control pain via multiple combined effects, have gained increasing popularity in the management of chronic neuropathic pain disorders. Only a few recent retrospective studies assessing the efficacy and safety of these medications have mentioned suspected allergic cutaneous reactions.^{62,63} In 2015, Turrentine et al⁶⁴ reported a case of ACD to cyclobenzaprine in a compound containing ketamine 10%, diclofenac 5%, baclofen 2%, bupivacaine 1%, cyclobenzaprine 2%, gabapentin 6%, ibuprofen 3%, and pentoxifylline 3% in a proprietary cream base. When patients present with suspected ACD to a compounded pain medication, obtaining individual components for patch testing is key to determining the allergic ingredient(s). We suspect that we will see a rise in reports of ACD as these topical compounds become readily adopted in clinical practices.

Patch Testing for Diagnosis

When patients present with symptoms concerning for ACD to medicaments, the astute clinician should promptly stop the suspected topical medication and consider patch testing. For common allergens such as neomycin, bacitracin, or ethylenediamine, commercial patch test preparations exist and should be used; however, for drugs that do not have a commercial patch test preparation, the patient's product can be applied as is, keeping in mind that certain preparations (such as retinoids) can cause irritant patch test reactions, which may confound the reading. Alternatively, individual ingredients in the medication's formulation can be requested from the manufacturer or a compounding pharmacy for targeted testing. Suggested concentrations for patch testing based on the literature and expert reference are listed in the Table. The authors (M.R., A.R.A.) frequently rely on an expert reference⁶⁶ to determine ideal concentrations for patch testing. Referral to a specialized patch test clinic may be appropriate.

Final Interpretation

Although their intent is to heal, topical medicaments also can be a source of ACD. The astute clinician should consider ACD when topicals either no longer seem to help the patient or trigger new-onset dermatitis. Patch testing directly with the culprit medicament, or individual medication ingredients when needed, can lead to the diagnosis, though caution is advised. Stay tuned for part 2 of this series in which we will discuss ACD to topical steroids, immunomodulators, and anesthetic medications.

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