STUDY

Allergens in Corticosteroid Vehicles

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Background: **Whereas allergy to vehicle ingredients (ie, excipients and preservatives) in topical steroid vehicles is well recognized, there are no data regarding which vehicle ingredients are in common use or on which vehicles and active molecules are associated with which ingredients.**

Objective: **To produce descriptive data on the use of allergenic vehicle ingredients in prescription topical corticosteroids.**

Methods: **The package insert for every steroid in widespread use in the United States was obtained from the manufacturer and used to generate an ingredient list for the product.**

Results: **There are seven vehicle ingredients that are commonly used in topical corticosteroid vehicles that are well-known allergens: propylene glycol, sorbitan sesquioleate, formaldehyde-releasing preservatives, parabens, methylchloroisothiazolinone/methylisothiazolinone, lanolin, and fragrance. Of 166 topical corticosteroids, 128 (including all creams) had at least one of these vehicle ingredients. More generic products were free of allergens than were branded products. Solutions and ointments were the least allergenic vehicles. The most commonly present potential allergens were propylene glycol and sorbitan sesquioleate.**

Conclusions: **Most prescription topical corticosteroids have the potential to cause allergic contact dermatitis owing to vehicle ingredients. Dermatologists should be aware of this possibility and should consider prescribing agents that do not contain potentially allergenic vehicle ingredients.**

ALLERGIC CONTACT DERMATITIS (ACD) is a common problem in dermatologic practice, but the prevalence of ACD from topical corticosteroid products is unknown. ACD from topical corticosteroid products can be due to an allergy to the active steroid in the product or allergy to ingredients in the vehicle. Steroids were the American Contact Dermatitis Society Allergen of the Year in 2005, and allergy to steroids and cross-reactivity among different steroids were recently reviewed.[1,2] ACD from ingredients in corticosteroid vehicles, on the other hand, has not been systemically examined.

In the present study, data on all widely dispensed generic and branded steroids were assimilated, and the vehicle ingredients were examined. The frequency with which allergens were present was determined, and patterns of vehicle ingredient use were analyzed. Based on the findings, it is clear that patients are frequently exposed to well-known allergens in topical corticosteroid vehicles. Recommendations for clinicians concerned about allergy to topical corticosteroid products are provided.

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Methods

The total number of units of topical steroid sold by manufacturers from September 2005 through September 2006 was obtained from the IMS National Sales Perspective Audit Moving Annual Total September 2006, a report that tabulates the number of units of each individual product sold by manufacturers to retail pharmacies and into nonretail channels.

To limit the analysis to products that are widely dispensed, further analysis was limited to products that sold at least 20,000 units from September 2005 to September 2006. Considering only such products, the total number of units of generic steroid sold was 44,087,465, and the total number of units of branded steroid sold was 4,826,387.

For each product, the manufacturer was contacted to obtain the full prescribing information. There were four generic products for which the package insert could not be obtained, and these were excluded from further analysis.

Based on the package insert, each product was assigned to one of the following groups: branded ointment, branded cream, branded liquid (throughout this article, solutions and lotions were combined under the term ''liquid''), branded gel, branded miscellaneous (foam, shampoo, tape,

spray), generic ointment, generic cream, generic liquid, and generic gel (there were no generic products classified as miscellaneous). The full ingredient list for each product was extracted from the package insert. The data were entered into a Microsoft *Excel* (Microsoft, Seattle, Wash) spreadsheet.

Six ingredients were identified as being significant on the basis of the following criteria: (1) the allergen is reported to cause positive patch-test reactions in at least 0.5% of patients patch-tested by the North American Contact Dermatitis Group (NACDG) or the Mayo Clinic group, and (2) the allergen is present in two or more topical corticosteroid products. These allergens are propylene glycol, formaldehyde-releasing preservatives, parabens, lanolin, sorbitan sesquioleate, and methylchloroisothiazolinone/methylisothiazolinone. Of note, a single product, Dermasmoothe FS (Hill Dermaceuticals, Sanford, FL), lists fragrance as an ingredient. Because this was the only product that contained fragrance, fragrance was not included in further analysis.

Filters were used to tabulate the number of products in each group that contained each of the potentially allergenic vehicle ingredients. Products containing vehicle ingredients that are likely to cross-react with any of the above allergens were treated as though they contained the allergen. Data on likely cross-reactors for each allergen were obtained from the Contact Allergen Replacement Database (CARD), which was accessed on January 28, 2007.

Results

Forty-six branded products were included in the analysis. These included 18 creams, 8 ointments, 12 liquids, 2 gels, and 6 miscellaneous products (2 foams, 1 tape, 1 shampoo, and 2 sprays). One hundred twenty generic products were included in the analysis. These included 52 creams, 40 ointments, 19 liquids, and 9 gels.

A significant majority of products (127 of 166) contained at least one of the analyzed allergens; 128 of 166 contained at least one allergen if fragrance is included. Overall, of the classes of vehicles, liquids were the least likely to contain an allergen, as 52% (16 of 31) of the liquids contained at least one of the analyzed allergens. Creams were the most allergenic, as 96% (67 of 70) of the creams contained at least one of the analyzed allergens.

Branded ointments were more likely to contain at least one of the analyzed allergens than were generic ointments: 87% (7 of 8) of branded ointments contained at least one of the analyzed allergens whereas 60% (24 of 40) of generic ointments contained at least one of the analyzed allergens.

Propylene glycol was the most commonly present allergen, being present in 64% (106 of 166) of products. It was present in at least one product of every vehicle type. It was especially common in branded ointments (6 of 8 products) and in gels (2 of 2 branded gels and 8 of 9 generic gels).

Sorbitan sesquioleate, or a potential cross-reactor with sorbitan sesquioleate (polysorbates and sorbitan monostearate are two examples of potential cross-reactors with sorbitan sesquioleate), was the second most common allergen, being present in 28% (47 of 166) of products. It also was present in at least one product of every vehicle type. It should be noted that in this study, we used the cross-reactivity approach that is used by CARD, which is a highly conservative approach. This is especially true in regard to sorbitan sesquioleate, for which many substances are considered potential cross-reactors, based on the fact that they contain a sorbitan or sorbate moiety, whereas in reality there are few or no data to demonstrate that they truly are cross-reactors in the clinical setting. However, we agree with this conservative approach as it makes little sense to accept the presence of possible cross-reactors when there are alternatives available that do not contain possible cross-reactors.

Tables 1 and 2 contain a complete tabulation of the allergens in generic and branded products. Table 3 contains a summary of the findings for each potential allergen.

Discussion

It is clear from our analysis that exposure to allergens via topical corticosteroid vehicles is a common and widespread occurrence. It is important that physicians are cognizant of this risk and that allergy to steroid vehicles be considered when a patient does not respond as expected to treatment with topical steroids. A working understanding of the various allergenic vehicle ingredients can be of significant benefit to the practicing dermatologist, and we will briefly review each of the allergens present in steroid vehicles.

In addition, practitioners should understand the regulations regarding generic topical corticosteroid products. Manufacturers must demonstrate that a generic product is bioequivalent to an existing Food and Drug Administration–approved product (typically a branded product). That is, the active pharmaceutical ingredient must be identical, and the two drugs must have the same rate and extent of delivery ($\pm$ 20%) as measured in a vasoconstrictor assay. Vehicles need not be identical, and often the vehicle is purposely different from that of the originally approved product in order to avoid patent infringement of the branded reference product.

Table 1. Summary of Commonly Allergenic Excipients* in Branded Topical Steroids†

Allergenic Excipient	*All Branded Products*	*Branded Creams*	*Branded Ointments*	*Branded Liquids*	*Branded Gels*	*Branded Miscellaneous*‡
Propylene glycol	28/46	12/18	6/8	5/12	2/2	3/6
Formaldehyde(s)	4/46	3/18	0/8	1/12	0/2	0/6
Sorbitan sesquioleate	10/46	4/18	2/8	2/12	0/2	2/6
Parabens	7/46	4/18	0/8	2/12	0/2	1/6
Lanolin	3/46	2/18	1/8	0/12	0/2	0/0
MCI/MI	1/46	1/18	0/8	0/12	0/2	0/0
None of the above	10/46	0/18	1/8	6/12	0/2	3/6

MCI/MI = methylchloroisothiazolinone/methylisothiazolinone.
*Defined as excipients to which at least 0.5% of patch-tested patients are reported to react positively.
†Only products that sold over 20,000 units between September 2005 and September 2006 were included.
‡Foams, tapes, shampoos, and sprays.

Propylene glycol is an odorless, colorless, and viscous aliphatic alcohol commonly used because of its solvent, humectant, and preservative qualities.[3] Some topical medications contain greater than 50% propylene glycol.[4] The most recently reported NACDG data indicated that 4.2% of patients reacted positively to patch testing with 30% propylene glycol in water.[5] The prevalence of allergy to propylene glycol has been called into question, however, as there is some indication that a 30% concentration, as used by the NACDG, may cause a significant number of irritant patch-test reactions.[6]

Fowler found that propylene glycol was present in 48 (59%) of 82 various corticosteroid creams, gels, ointments, and liquids sold in the United States in 1993.[7] It has become slightly more widely used in prescription topical corticosteroids over the last 14 years and is currently present in 64% (106 of 166) of products. It can be present in any type of corticosteroid vehicle.

Sorbitan sesquioleate (SS) is an emulsifier used in corticosteroid ointments. Emulsifiers are agents that allow normally immiscible substances, such as oil and water, to combine and form a stable mixture. SS is not tested by the NACDG, but the senior author has seen several positive reactions to this allergen, all of which have been relevant, and the Mayo Clinic group found that 5 (0.8%) of 610 tested patients had positive reactions to this allergen.[8] It is in common use in topical steroids and can be present in products of any vehicle type.

Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) is a mixture of two preservative isothiazolinones used in cosmetics and in industrial liquids, such as metalcutting liquids. It has a broad spectrum of activity against fungi and against gram-positive and gram-negative bacteria.[3,4] The NACDG found 2.3% of tested patients to be allergic to this compound in their most recently reported data.[5] MCI/MI was found only in topical corticosteroids containing halobetasol as an active ingredient.

Lanolin is a complex oily material secreted by the sebaceous glands of sheep. It coats wool and is obtained from wool after shearing. Lanolin is used in cosmetics and pharmaceuticals because of its emollient, moisturizing, and emulsifying properties. Numerous purifications and

Table 2. Summary of Commonly Allergenic Excipients* in Generic Topical Steroids†

Allergenic Excipient	*All Generic Products*	*Generic Creams*	*Generic Ointments*	*Generic Liquids*	*Generic Gels*
Propylene glycol	78/120	38/52	22/40	10/19	8/9
Formaldehyde(s)	7/120	7/52	0/40	0/19	0/9
Sorbitan sesquioleate	37/120	21/52	9/40	6/19	1/9
Parabens	12/120	9/52	1/40	2/19	0/9
Lanolin	7/120	6/52	1/40	0/19	0/9
MCI/MI	2/120	2/52	0/40	0/19	0/9
None of the above	29/120	3/52	16/40	9/19	1/9

MCI/MI = methylchloroisothiazolinone/methylisothiazolinone.
*Defined as excipients to which at least 0.5% of patch-tested patients are reported to react positively.
‡Only products that sold over 20,000 units between September 2005 and September 2006 were included.

Table 3. Summary of Findings for Each Ingredient

Ingredient	*Summary of Findings*	*Most Recently Reported Prevalence of Patch-Test Reactions (%)*
Propylene glycol	Most common allergen in steroid vehicles Can be found in any vehicle	4.2
Sorbitan sesquioleate	Second most common allergen in steroid vehicles Can be found in any vehicle	0.8
MCI/MI	Found only in products with halobetasol as active ingredient	2.3
Lanolin	Creams and ointments only	2.2
Parabens	Primarily in creams and liquids	0.6
Formaldehyde-releasing preservatives	Imidazolidinylurea and diazolidinylurea Primarily in creams	3.2 (diazolidinylurea) and 3.0 (imidazolidinylurea)

MCI/MI = methylchloroisothiazolinone/methylisothiazolinone.

modifications of lanolin can improve its spectrum of use and minimize the likelihood of a type IV allergic reaction to it. According to the most recent NACDG data, 2.2% of tested patients reacted to lanolin.[5] Lanolin was found in creams and ointments in the present study.

Parabens are alkyl esters of p-hydroxybenzoic acid. They are commonly used preservatives, both in prescription and over-the-counter topically applied products. Each ester has different antimicrobial properties, but they generally all tend to be more effective against fungi than against bacteria. Because of this property, they are commonly used with other preservatives, such as imidazolidinylurea, to achieve greater activity against the gram-negative bacterium *Pseudomonas aeruginosa*.[4] The NACDG reported that 0.6% of patients reacted to the paraben mix according to their most recent data.

Allergy to parabens is a complex topic. In the past, parabens were used at high concentrations in topical medications applied to eczematous lesions or stasis ulcers and commonly caused hypersensitivity reactions. Most topical medications now exclude parabens because of a high rate of contact allergy when paraben-preserved products are applied to inflamed skin; in cosmetics, however, parabens are the second most common ingredient.

Paraben-preserved products infrequently cause contact allergy when applied to noninflamed skin, even in sensitized patients. In addition, false-negative patch-test results can occur when patch testing is carried out on noninflamed skin of the back whereas the same patient can have clinically significant ACD when a paraben-preserved product is applied to inflamed skin. These two phenomena are known as the ''paraben paradox.''[9] In our study, parabens were primarily found in creams and liquids.

Two formaldehyde-releasing preservatives, imidazolidinylurea and diazolidinylurea, are commonly used in topically applied products as preservatives. They are particularly effective against bacteria such as *Pseudomonas aeruginosa* and are less effective against fungi.[4] Diazolidinylurea releases more formaldehyde than does imidazolidinylurea and is therefore more likely to cause ACD in formaldehyde-allergic patients. It should also be noted that patients can be allergic to imidazolidinylurea or diazolidinylurea without being allergic to formaldehyde, so if only formaldehyde is used to screen for allergy to these agents, some cases will be missed. Citing their most recent data, the NACDG reported that at least 3.2% of patients reacted to diazolidinylurea and that at least 3.0% of patients reacted to imidazolidinylurea.[5] In our study, imidazolidinylurea was more commonly present in topical corticosteroids than was diazolidinylurea. Both were primarily found in creams.

It should be noted that it is somewhat surprising that MCI/MI or formaldehyde-releasing preservatives would be used in a steroid preparation that is intended to be applied to inflamed skin. These are fairly strong sensitizers, especially MCI/MI, and it is conceivable that their use in a preparation that is applied to inflamed skin could entail a risk of sensitizing patients.

Conclusion

When a clinician suspects that a patient may have allergic contact dermatitis (ACD) from a corticosteroid, there are two possible culprits: the steroid molecule itself, or an inactive ingredient in the vehicle. We have shown that the significant majority of topical corticosteroids contain at least one potential allergen in their vehicle, that all types of vehicles can contain allergens, and that certain allergens are found in association with particular active ingredients. In terms of allergy to steroid molecules, the steroids are divided into four classes: classes A, B, C, and D. Patch-test reactions

Table 4. Topical Products Recommended for Empiric Use in Settings of Suspected Steroid Allergy*

A. Nonallergenic active ingredient, nonallergenic vehicle
  a. Topicort Ointment (desoximetasone 0.25% ointment, Taro Pharmaceuticals)
  b. Topicort Gel (desoximetasone 0.5% gel, Taro Pharmaceuticals)
  c. Protopic Ointment (tacrolimus 0.1%, 0.03% ointment, Astellas Pharma)
B. Nonallergenic vehicle, potentially allergenic active ingredient
  a. Ointments
    i. Locoid Ointment (hydrocortisone butyrate 0.1% ointment, Ferndale Labs)
    ii. Generic triamcinolone 0.1% ointment
    iii. Generic desonide 0.05% ointment
  b. Liquids
    i. Locoid Lotion (hydrocortisone butyrate 0.1% lotion, Ferndale Labs)
    ii. Beta-Val Lotion (betamethasone valerate 0.1% lotion, Teva Pharmaceuticals)
    iii. Embeline Lotion (clobetasol propionate 0.05% lotion, Coria Labs)
    iv. Cormax Lotion (clobetasol propionate 0.05% lotion, Watson Labs)
    v. Generic clobetasol 0.05% lotion
    vi. Generic betamethasone dipropionate 0.05% lotion
C. Nonallergenic steroid, potentially allergenic vehicle
  a. Cloderm Cream (clocortolone 0.1% cream, Coria Labs); contains parabens

*Where generic products are recommended, all generic products with that active ingredient that were included in our analysis met the listed criteria.

to class A steroids are most common (3.0% of tested patients); reactions to class B and class D steroids are less common (1.1% and 0.5%, respectively) whereas patch-test reactions to class C steroids are extremely rare. This classification was recently reviewed by Jacob and Steele.[2]

Several recommendations can be made to clinicians who are concerned that a particular patient may be allergic to topical corticosteroid preparations. First, if patch testing is not available and the clinician has a high suspicion of ACD from topical corticosteroids, then the clinician should prescribe a class C steroid with a vehicle that contains no allergens. Topicort Ointment (desoximetasone 0.25% ointment, Taro Pharmaceuticals, New York, NY) and Topicort Gel (desoximetasone 0.05% gel, Taro Pharmaceuticals) are the only two products that meet these criteria. Protopic Ointment (tacrolimus 0.1%, 0.03% ointment, Astellas Pharma, Deerfield, IL) is another appropriate empiric choice as its vehicle contains no allergens and it is not a steroid. Further recommendations are given in Table 4.

Second, patch testing should be undertaken if possible. At a minimum, the patient should be tested against propylene glycol, sorbitan sesquioleate, formaldehyde, imidazolidinylurea, diazolidinylurea, paraben mix, fragrance mix, lanolin, MCI/MI, and the following steroid allergy screening agents: tixocortol pivalate (a class A screening agent), budesonide (a class B screening agent), and hydrocortisone butyrate (a class D screening agent). As several of these allergens are not present on the Thin-Layer Rapid Use Epicutaneous (T.R.U.E.) Test (Allerderm Labs, Phoenix, AZ), dermatologists using the T.R.U.E. Test system should consider supplementation with additional allergens. After patch testing, topical steroid preparations to which the patient is not allergic can be selected, based on the results.

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