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When the Treatment is the Culprit: Prevalence of Allergens in Prescription Topical Steroids and Immunomodulators

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Title: When the Treatment is the Culprit: Prevalence of Allergens in Prescription Topical Steroids and Immunomodulators

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Prescription topical corticosteroids (TCS) and immunomodulators (TIMs) are commonly used for various dermatological conditions. They may be a frequent source of medicament dermatitis due to widespread use and sensitizing ability.^{1,2} Physicians should have a high suspicion for ACD to topical medicaments when a corticosteroid-sensitive dermatitis fails to respond or worsens after therapy. This study reports a comprehensive analysis of potential allergens in prescription TCS and TIMs in the current US market.

This study queried for commonly reported contact allergens in prescription TCS and TIMs in a one-week period from March 19 - March 26, 2019 using DailyMed, the official provider of up-to-date FDA label information. Inclusion criteria included prescription-only topical corticosteroids, calcineurin inhibitors and topical PDE4 inhibitor. Exclusion criteria included combination drugs and over-the-counter topical steroids including hydrocortisone. Ingredient and vehicle formulation data was abstracted. The prevalence of each potential allergen and product distribution by vehicle was determined.

A total of 746 TCS products were analyzed. A total of 73.6% (549/746) TCS products contained at least one allergen. The prevalence of allergens found in our study was compared to current reported positive reaction rates (PRR) as recorded in Table I. Propylene glycol (PG) was the most common allergen found (56.6%; 422/746). Table II shows all of the TCS queried that did not contain PG by potency class. Betamethasone dipropionate was found as two formulations: betamethasone dipropionate or augmented betamethasone dipropionate. Out of 62 betamethasone dipropionate products, all products labeled as augmented contained PG (39%; 24/62). Parabens, which are commonly used preservatives, were found in 18.6% (133/746) of prescription TCS.

15.3% (114/746) of products contained multiple parabens and 2.6% (19/746) of products contained only one paraben, which was methylparaben alone. A total of 2.7% (20/746) of products contained at least one formaldehyde releasing preservative (DMDM hydantoin, diazolidinyl urea, or imidazolidinyl urea). Isothiazolinones were found in all halobetasol propionate 0.05% creams with MCI/MI found in 6/8 and MI alone in 2/8 products. Vehicles that more commonly contained an allergen included creams (90%; 326/362), lotions (79%; 50/63), topical solutions (64%; 32/50), gels (76%; 19/25), foams (100%; 23/23), and shampoos (100%; 7/7).

A total of 12 TIMs products (pimecrolimus cream 1%, tacrolimus ointment 0.03% and 0.1%, and crisaborole) was queried. Propylene glycol was found in 5/11 products (45.5%). Tacrolimus ointment 0.03% and 0.1% did not contain any allergens. Crisaborole ointment 2% contained propylene glycol.

The majority of prescription TCS and TIMs contain at least one potential allergen in the vehicle. PG is an important potential contact allergen to recognize, given its prevalence in prescription topicals and increasing incidence of allergy over time.³ The presence of MCI/MI in TCS has high clinical concern given the epidemic of contact allergy. Importantly, all formulations of halobetasol cream 0.05% contained an isothiazolinone. The knowledge of potential allergens in prescription topicals in relation to PRR is useful for physicians to develop clinical suspicion for medicament ACD and refer early to a patch testing specialist to identify relevant allergens.

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Table I. This table provides the prevalence of allergens in current prescription TCS and reported positive reaction rates (PRR) based on NACDG reports and literature review.³ Note that the PRR used for comparison are not rates of these allergens in formulation of prescription topicals alone, and represent total sensitization rates in those patch tested by the NACDG. The majority of positive reactions to phenoxyethanol and sorbic acid are reported as case reports with estimates of 0.34% and 0.33%, respectively.^{4,5} Given that SSO is the most commonly tested, the positive reaction rate for sorbitan derivatives as a group was determined to be the prevalence of SSO alone at 0.2%.⁶

Table II. Prescription Topical Corticosteroids without Propylene Glycol by Potency Class based on FDA ingredient labels queried in DailyMed from March 19 to March 26, 2019. Formulations may vary over time, thus checking labels is always recommended.

98 **Table I.** Prevalence of Allergens in Prescription Topical Corticosteroids and Reported Positive
99 Reaction Rates

Allergen	Percent of Total Products (%)	Positive Reaction Rates (%)
Propylene glycol	56.6	4.0
Sorbitan derivatives	26.8	0.2
Parabens	18.6	0.6
Sorbic acid	13.3	0.3
Lanolin	8.4	4.1
Sorbitan sesquioleate (SSO)	5.6	0.2
Imidazolidinyl urea	2.2	1.1
Diazolidinyl urea	1.2	1.2
Cocoamidopropyl betaine	0.9	1.6
MCI/MI	0.8	7.3
Phenoxyethanol (PE)	0.4	0.3
MI	0.3	13.4
DMDM hydantoin	0.3	0.8

101 **Table II.** Prescription Topical Corticosteroids without Propylene Glycol by Potency Class

Generic Name	Formulation
<i>Class 1 (super-potent)</i>	
Clobetasol propionate	Solution 0.05% Spray 0.05% Shampoo 0.05%
Desoximetasone	Spray 0.25%
Fluradrenolide	Tape 4mcg/cm ²
Halobetasol propionate	Cream 0.05%
<i>Class 2 (high potency)</i>	
Desoximetasone	Cream 0.25% Gel 0.05% Ointment 0.25%
Halcinonide	Ointment 0.1%
Triamcinolone acetonide	Ointment 0.5%
<i>Class 3 (high potency)</i>	
Betamethasone valerate	Ointment 0.1%
<i>Class 4 (medium potency)</i>	
Desoximetasone	Cream 0.05% Ointment 0.05%
Flurandrenolide	Ointment 0.05%
Fluocinolone acetonide	Ointment 0.025%
Triamcinolone acetonide	Ointment 0.1% Topical spray (0.147 mg/g)
Betamethasone dipropionate	Spray 0.05%
<i>Class 5 (medium potency)</i>	
Betamethasone valerate	Lotion 0.1%
Clocortolone pivalate	Cream 0.1%
Flurandrenolide	Lotion 0.05%
Fluocinolone acetonide	Topical 0.01% (Scalp oil)
Hydrocortisone butyrate	Cream 0.1% Lotion 0.1% Ointment 0.1% Solution 0.1%
Triamcinolone acetonide	Ointment 0.025%
<i>Class 6 (low potency)</i>	
Desonide	Ointment 0.05%
Fluocinolone acetonide	Topical 0.01% (Scalp oil)
<i>Class 7 (least potent)</i>	
Hydrocortisone	Topical solution 2.5% Ointment 2.5%