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Clinical and Economical Considerations in Topical Corticosteroid Selection

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Practical Aspects of Topical Corticosteroid Selection

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Topical therapy is ideally suited for the management of skin diseases. The potential benefits of topical drug therapy are numerous, including local targeted treatment, reduced systemic drug exposure, and subsequent reduced risk of systemic side effects. However, while topical therapy may offer convenience and safety, topical drug delivery is no simple exercise, since the stratum corneum is one of the most difficult barriers to overcome.

As specialists in the treatment of skin diseases, dermatology providers recognize that numerous variables can influence the delivery of drugs through the stratum corneum. The epidermal barrier is efficient in its exclusion of toxins, irritants, allergens, and any other foreign bodies, including topical drugs. The amount of topical drug that passes through the stratum corneum is generally low. The rate and extent of absorption vary depending on the characteristics of the active agent, as well as on the vehicle.

The epidermal barrier may be impaired in many inflammatory dermatoses.[1] Therefore, topical drugs must be formulated to encourage efficient delivery of active agents without contributing to further degradation of the epidermal barrier. In fact, an ideal formulation will *support* barrier repair in efforts to arrest the disease process.

With these considerations in mind, dermatology providers understand the importance of vehicles in topical drug therapy. In the past, formulators emphasized drug delivery, sometimes to the detriment of barrier integrity, leading to the marketing of alcohol-based gels and creams with relatively high levels of so-called "penetration enhancers"— ingredients that temporarily disrupt the skin barrier, fluidize the lipid channels between corneocytes, alter the partitioning of the drug into skin structures, or otherwise enhance delivery into skin. While the presence of penetration enhancers within a formulation is not inherently objectionable, certain chemicals and high levels of any enhancer can contribute to further barrier degradation, which in turn worsens the very condition we are treating.

Today, innovations in the formulation sciences have led to a better balance between drug delivery and barrier support. This innovation is largely characteristic of brand-name drug developers, whose investments in formulation development have led to novel and highly efficient vehicle bases and delivery systems. It has been suggested that some generic manufacturers have actually increased their reliance on outmoded delivery systems in their efforts to inexpensively approximate the efficacy of reference drugs.[2]

In the current healthcare market place, however, it is not always easy to prescribe branded drugs. Therefore, it has become important to understand the approval process for generic topical steroids, one of the most commonly prescribed products in our practices. Generic drug approval requires that generics match active ingredients, concentration, and dosage, but not the formulation.[2] They also have to demonstrate significant bioequivalence to the reference listed drug, which is the branded drug. The Food and Drug Administration defines significance as 20% within 90% confidence interval. If you do the math, you'll see that the accepted bioequivalence range is 45%, which is an amazingly wide spectrum.

However, unlike any other drug, generic topical steroids do not have to show bioequivalence in clinical trials. They only have to show bioequivalence in the vasoconstrictor assay, which is performed on the volar forearm of normal skin. In fact, generic topical corticosteroid formulations do not have to show clinical therapeutic effects, since they have never been tested on diseased skin or an impaired epidermal barrier. As already mentioned, the generic formulation need not

"Wouldn't it be nice to have a generic formulation that is exactly the same as the branded formulation?"

contain the same excipients as the reference formulation, nor must it demonstrate equivalent tolerability. Actually, the generic formulations need not be tested for tolerability.

Thus, we all face the dilemma of treating our patients with a generic that is, at best, close to the branded product. But this too has become an impossible task because there are so many different generics with different formulations. Therefore, the truth is, we have no control over the treatment we are prescribing.

Wouldn't it be nice to have a generic formulation that is exactly the same as the branded formulation?

This is where products such as Desoximetasone 0.05% ointment or Desoximetasone 0.25% ointment come into the picture, where both branded and generic are produced by the same manufacturer. For example, both branded and generic Desoximetasone 0.05% ointment are exactly the same, with the same excipients in the vehicle. More importantly, no other generic of this product exists. Therefore, this is one time I am in support of generic substitution!

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Not All Topical Corticosteroids are Created Equal! Optimizing Therapeutic Outcomes Through Better Understanding of Vehicle Formulations, Compound Selection, and Methods of Application

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ABSTRACT

Since the first successful topical glucocorticosteroid, compound F, was applied to human skin to treat eczematous dermatitis approximately 60 years ago, several advances have been made in the development of topical corticosteroid (TC) compounds and vehicle formulations.[1-3] The ability to apply a TC and improve skin disease revolutionized dermatologic therapy and has proven to be one of the biggest advances in the history of dermatology. The potency of a TC and their vehicle formulation can vary among brand and generic TC compounds, which can sometimes confound the clinical situation as one brand or generic formulation of a given TC may be well tolerated while another generic formulation induces skin irritation or allergenicity in a patient who previously encountered no difficulties.

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INTRODUCTION

The need for a topically-applied therapeutic agent to be in its active form and to achieve access in adequate concentration at its target site(s) of action set the stage for understanding the pharmacokinetic and pharmacodynamic principles that underscore the development of a therapeutically successful topical corticosteroid (TC) compound and formulation. We now know that corticosteroids induce a broad range of anti-inflammatory, antiproliferative, and immunosuppressive effects that are therapeutically beneficial with topical application for a variety of skin disorders if used appropriately.[2,3] However, many of these same effects can lead to adverse events (AEs) with prolonged use and inadequate professional supervision. Intracellularly, TCs produce their effects by binding to cytoplasmic glucocorticoid receptors (GRs), which traverse into the nucleus, bind to response elements within steroid-responsive genes, and lead to either transrepression or transactivation of regulatory proteins.[3] Anti-inflammatory effects are modulated primarily by transrepression of cyclooxygenase-2 (COX-2) or specific cytokines. Many TC-related AEs appear to be caused by transactivation of specific pathways.[3]

The ability to induce receptor interactions and cellular effects is not enough to achieve therapeutic results after TC application. The TC must be formulated in a vehicle that allows for percutaneous penetration and that patients also find acceptable when applying it to their skin. Over time, advances in vehicle formulation science have led to many improvements such as greater percutaneous penetration of the active ingredient, increase in TC potency, and improved physical characteristics of the formulation.[2-4] However, at the end of the day, the most effective TC in a given patient is the one that is properly matched in potency to the disease state being treated, is least likely to induce irritant or allergic reactions to the active or inert ingredients in the formulation, and is cosmetically pleasing to the patient upon application.

The Current Position of Topical Corticosteroids in Dermatology

The ability to apply a TC and improve skin disease revolutionized dermatologic therapy and has proven to be one of the biggest advances in the history of dermatology. In addition to common dermatoses—such as eczematous dermatitis, seborrheic dermatitis (SD), and psoriasis—TCs have been used effectively to treat a wide variety of corticosteroid-responsive dermatoses (CRDs). Although the efficacy of TC therapy may vary with some disease states, properly selected TC therapy has been highly effective in reducing flares of many dermatologic disorders, especially the eczematous dermatoses, such as atopic dermatitis (AD) and contact dermatitis, SD, and psoriasis.[2-4] The many disease states in which TCs have been used with reasonable success are reviewed elsewhere; however, the most common applications are AD, nummular eczema, irritant contact dermatitis, allergic contact dermatitis, SD, and chronic plaque psoriasis.[2,3]

Importantly, TC therapy, in addition to being efficacious in many clinical circumstances for a variety of disorders, has also proven to be very safe when used appropriately and when properly supervised.[2-5] The clinically relevant AEs of TC use include dermal atrophy, epidermal barrier impairment, striae, TC-induced rosacea-form eruption, TC-induced perioral dermatitis, and contact sensitization.[2,3] However, AEs associated with TCs are uncommon when TC therapy is used with the recommended frequency and duration, and supervised by a clinician who knows its proper use and monitors patients appropriately. In fact, poor adherence to TC therapy, or use of a TC that is not sufficiently potent for the disorder, often leads to a prolonged skin eruption with its associated symptoms (such as AD and pruritus). In some cases, poor adherence is due to clinicians and/or other health care professionals overstressing the possible TC-related AEs to patients or to parents of children with AD. This

over-emphasis feeds into an exaggerated fear of using TCs, referred to as "steroid phobia".[7] In one study, approximately 81% of patients seen at a dermatology clinic indicated they had fears of using a TC, and 36% admitted poor compliance with their prescribed TC treatment.[7] This is unfortunate, as in many cases the adverse sequelae are more problematic when TC therapy is not used than when it is used appropriately and under proper supervision.[4-7]

In addition to "steroid phobia," which is not uncommon, especially in parents of children with AD, other challenging clinical scenarios associated with TC use currently include:

- differentiation between various brand products and formulations with regard to the active ingredient and/or vehicle characteristics
- differentiation between brand and generic formulations with regard to vehicle characteristics
- avoidance of AEs in patients needing repeated or prolonged courses of therapy due to the chronicity of their disease
- incorporation of adjunctive therapies along with TC therapy to optimize efficacy, reduce potential AEs, and decrease the frequency and intensity of relapses
- methods to sustain the therapeutic benefit once a disorder that is chronic and relapsing in nature is brought under control with TC therapy
- cost considerations and access to selected TC products

Many of these challenges are addressed in this article.

Differentiation of Topical Corticosteroid Formulations

The three major factors that influence the pharmacokinetic profile and comparative potency of a given TC formulation are the corticosteroid compound (active ingredient), the vehicle formulation, and the characteristics of the skin to which the TC is applied.[2,3]

Corticosteroid Compound

The inherent lipophilicity, solubility, ability to penetrate percutaneously, and relative GR binding activity of a corticosteroid compound relates to specific characteristics of its chemical structure, especially modifications at certain positions within the corticosteroid structural nucleus.[2,3] For example, replacing a hydroxyl group with a chloro moiety converts the lower potency TC betamethasone to the superpotent TC clobetasol.[8,9] This serves as one example of how structural modification of corticosteroids can potentially alter the physiochemical nature of the compound in many ways that are clinically relevant. The relative potency of TC formulations has classically been assessed using the Stoughton vasoconstrictor assay, which often correlates with the potency observed in clinical practice; however, exceptions do exist.[2-4] In reality, the use of a TC formulation (including consideration of its vehicle properties) in well-designed clinical trials is important in determining "real world" potency, as is its correlation with the disease state being treated.

The significance of the TC compound itself extends beyond the physiochemical properties of the active agent. Allergic sensitization to TCs occurs, and it varies in frequency depending on the chemical structure of the TC compound, with TCs separated into class designations based on their structural characteristics and tendency to induce contact allergy.[2-4,10,11] The break-down, examples of TCs in each class, and reported prevalence rates for TC-induced contact allergy are listed below:[2,12,13]

- Class A (hydrocortisone; 2.7%)
- Class B (triamcinolone, fluocinonide; 1.5%)
- Class C (desoximetasone, clocortolone pivalate; <0.2%)
- Class D1 (betamethasone dipropionate, betamethasone valerate, clobetasol propionate; 0.8%)
- Class D2 (hydrocortisone butyrate, hydrocortisone valerate; 0.8%)

Topical corticosteroid contact allergy is suspected when there is a poor response to treatment, an initial good response with a later lack of response, or the development of a worsening cutaneous eruption. Overall, the prevalence of allergic contact hypersensitivity to a TC is reported to range between 0.2% and 6%; although in one report of patients with a poor response to TC therapy 22% were shown to exhibit a TC allergy.[3,10] In patients who are compliant with TC use but their skin disorder still does not respond appropriately when a definite response is anticipated, both reconsideration of the diagnosis and the possibility of contact allergy from the TC formulation are to be considered. In addition to an allergy induced by the corticosteroid compound itself, an excipient ingredient in the TC vehicle may be the cause of allergic contact dermatitis. Allergy to the active corticosteroid ingredient or an excipient ingredient in the vehicle should be suspected in patients who are non-responsive or poorly responsive to TC therapy because 9% to 22% of such adults, and 25% of such children, have been shown to be allergic to the TC formulation.[12,13]

The subject of TC allergy is discussed in detail in this supplement and elsewhere in the literature.[2,10-13] Of importance to the clinician is that two TC active ingredients, desoximetasone and clocortolone pivalate, are essentially devoid of contact allergies.[10-13]

Vehicle Formulation

Vehicle formulations vary widely in their physical and chemical characteristics, and are often chosen in the clinical setting based on the anatomic site(s) and surface area of application.[2-4] The clinical relevance of vehicle formulation extends beyond the texture, spreadability, cosmetic eloquence, and other physical characteristics. In fact, some components of the vehicle can alter the pharmacokinetics of the active TC by increasing solubility (ie,

ethanol) and/or enhancing percutaneous penetration of the TC (ie, proplylene glycol in high concentration).[2,10] Other excipients affect the type of vehicle base, such as emulsifying agents used in oil-in-water-based creams or lotions, and solvents used to formulate non-viscous bases like solutions and gels.[2]

Importantly, the excipients chosen to be used in a TC vehicle formulation can cause cutaneous irritation or even contact allergy.[10-13] Although the active ingredient and its concentration may be the same in comparative formulations, the excipients can vary significantly between brand and generic products that use the same TC in the same vehicle type (ie, cream, ointment, lotion, etc).[2-4,10] The contents of the brand formulation of a TC are known and consistent, but the excipient ingredients among different generic formulations can vary.[2,10] This can sometimes confound the clinical situation as one generic formulation of a given TC may be very well tolerated while another induces skin irritation or allergenicity unexpectedly in a patient who encountered no prior difficulty. As a result, differences between brand and generic formulations must be considered, because the excipients in TC vehicles can directly influence the pharmacokinetic properties, cutaneous irritancy, allergenicity (to a given excipient), potency, therapeutic activity, and cosmetic acceptability.[2-4,8-13] In some cases, non-immunologically-induced contact urticaria can be caused by excipients such as sodium benzoate, sorbic acid, or balsum of Peru.[2,10]

Examples of excipients used in TCs that can induce contact allergy and their respective rates of contact allergenicity are the emulsifying agent sorbitan sesquioleate (≤10%), the commonly used parabens preservatives (1.2%), methylchloroisothiazolinone (2.8%), formaldehyde releasers (9%), the occlusive emollient lanolin (1.8%), and propylene glycol when used in high concentrations as a penetration enhancer (2.9%).[14,15] Propylene glycol is also commonly used in very low concentrations as a humectant, and in this scenario is less likely to induce skin allergenicity or cause cutaneous irritation. Although it has been noted that generic formulations will often contain more excipients than brand products, this may not always be the case. What clearly differs is that the ingredients in a brand TC product are consistent and known, whereas the excipient ingredients used in vehicles among generic formulations of TC products can vary substantially, potentially resulting in differences in clinical response and/or the emergence of irritant or allergic tolerability reactions at sites of application. Among TC formulations available in the US, only desoximetasone 0.25% and 0.05% ointment and desoximetasone 0.05% gel do not contain any ingredients listed in the "top 65 cutaneous allergens" by the North American Contact Dermatitis Group.[15]

Comparative Potency

Lastly, there are also examples documenting that the generic TC products are not necessarily therapeutically equivalent to the brand TC product, or to each other, and may differ in potency.[2,16] Ultimately, it is difficult for the clinician or patient to know what they are getting with a generic TC. In reality, many patients respond to therapy with generic TC agents; however, there are clearly some cases that are fraught with less than optimal results, either due to a suboptimal vehicle that compromises efficacy, or the inclusion of excipients that induce irritant or allergic skin reactions.

Anecdotally, the lead author (JDR) has noted poor efficacy with some generic formulations of topical fluocinonide and with generic clobetasol propionate 0.05% lotion. In some of these anecdotally-observed cases, the brand formulation produced effective results in patients who did not respond after use of a generic product that contained the same active ingredient, in the same concentration, and in the same vehicle type (ie, lotion, ointment). Interestingly, the reverse of this pattern has not been noted.

Methods to Achieve Control and Sustain the Therapeutic Benefit of Topical Corticosteroid Therapy

Adequate Potency and/or Tolerability

It is important to use a TC of adequate potency when initiating therapy to control the flare of an eruption. Certain disease states, such as SD, typically respond well to a low-potency to mid-potency TC, usually within days.[2,3,17,18] Eczematous dermatoses are more variable depending on severity and the extent of lichenification.[2-4] Chronic plaque psoriasis affecting non-intertriginous or non-facial areas usually warrants treatment with a high-potency to super-high-potency TC in order to achieve control of a flare.[2,3] With compliant use of TC therapy, most patients respond favorably. In children with AD, there is a tendency to undertreat their disorder with the use of a low-potency agent.[4] This may be reasonable in certain anatomic sites such as the face, axillae, and groin folds, but use of a higher potency TC over a short duration to more quickly achieve control of the AD flare, followed by the tapering of the TC potency and/or frequency of application, makes more sense and reduces frustration by not allowing the AD and associated pruritus to linger incessantly.[2,4]

Frequency of Application at Initiation of Therapy

Topical corticosteroids may be applied once or twice a day, once daily being helpful in increasing adherence.[2-4,19] In addition, when an ointment base is advantageous, such as in subacute to chronic AD or plaque psoriasis, once-daily application at night is more convenient and less messy than twice-daily application. Once-daily use appears to be equivalent to twice-daily use for eczematous dermatoses, especially when using a higher potency TC.[19] Once-daily use appears to be equivalent to twice-daily use, especially for eczematous dermatoses, and particularly with a higher potency TC.[19] Moreover, this approach allows for the use of other adjunctive therapies earlier in the day, such as barrier repair therapy in atopic patients or a vitamin D analog for psoriasis.[4,20,21] Also, it is very important to consider vehicle preferences, prescribe adequate amounts of medication, and provide proper education on the amount and method of TC application to prevent overuse or waste of product.[4,5,22]

Sustaining Therapeutic Benefit

Unfortunately, pivotal trials to gain approval of a TC are directed at control of disease exacerbation, with no direction on what to do thereafter. There is a strong consensus that abrupt discon-

tinuation of TC therapy once the skin eruption has cleared often leads to a more rapid relapse of many dermatologic disorders, including SD, AD, and psoriasis.[4,17,23] More optimal approaches are to taper the frequency of TC therapy and to "step down" to a lower potency, along with integrating adjunctive therapy where indicated.[4,18,23] The use of long-term intermittent TC therapy to sites previously affected by AD, as well as topical barrier repair therapy (BRT) to unaffected skin, is suggested for sustaining control of eczematous flares and prolonging the duration of remissions, and has been shown to be beneficial and safe in both children and adults.[4,23-26] The intermittent use of higher potency TCs along with a vitamin D analog is helpful in maintaining control of chronic plaque psoriasis.[27] This approach also appears to reverse some of the reduction in antimicrobial peptide proteins that may be associated with TC use.[21]

Topical corticosteroids have been shown to cause structural changes that are associated with an impaired permeability barrier function, such as decreased keratinocyte size, decreased ceramides, free fatty acids, and cholesterol; as well as increased tansepidermal water loss.[28] Therefore, it is important for a topical BRT to be integrated with TC therapy, especially for eczema-prone and atopic skin, in order to prevent rapid relapse and to prolong the duration of remission after the TC is stopped.[4,20,29-30]

CONCLUSION

Topical corticosteroids are vital to the practice of dermatology as these agents are effective and safe when properly used. However, not all TCs are created equal. There are several excellent choices in all potency categories, even though differences emerge between brand and generic formulations, depending on the quality of the vehicle used by the generic manufacturer. When considering concerns about TC-induced cutaneous allergy, desoximetasone and clocortolone pivalate are essentially free of risk for contact allergy. The excipients in desoximetasone ointment and gel are also associated with a negligible risk of inducing allergic sensitization.

DISCLOSURES

Dr. Del Rosso has served as a consultant, advisory board participant, clinical investigator, and speaker for Allergan, Bayer, Dermira, Eisai, Galderma, Medicis, Obagi Medical Products, Onset Dermatologics, Pharmaderm, Quinnova, Primus, Promius, Ranbaxy, Taro, TriaBeauty, Unilever, Valeant, and Warner-Chilcott.

Dr. Kircik has served as an advisor, investigator, consultant, and speaker for Bayer, Galderma, Promius, Stiefel, GSK, Leo, Taro, and Valeant.

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Allergy to Topical Steroids

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ABSTRACT

Topical steroid allergy (TSA), as defined by an allergy to either the steroid molecule itself or to an ingredient in the vehicle, is common in clinical practice, but it is rarely diagnosed. This article elucidates the difficulties involved in clinically recognizing TSA, and also the appropriate protocols for its diagnosis and treatment.

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INTRODUCTION

Based on recent results from the North American Contact Dermatitis Society, of 4,454 patients sent for patch testing nearly 10% were allergic to at least one substance that is used as a vehicle ingredient or an active ingredient in topical steroids.[1] A study from the Mayo Clinic showed that over 10% of patients reacted to at least one steroid.[2] When the group of patients considered is limited to those who have not responded as expected to topical steroids, because they did not improve or they deteriorated, up to 22% of patients have topical steroid allergy (TSA).[3]

Given the enormous amount of data collected over the last two decades demonstrating that TSA occurs frequently in dermatitis patients, it should be encountered commonly in clinical practice. However, the most common response encountered by the author when discussing or lecturing on TSA to practicing dermatologists has been that they have either never seen TSA or have seen it only very rarely in their patients. This discrepancy between the data conclusively demonstrating that TSA is common and the perception among clinicians that it is rare can be explained by four factors:

1. The exceptional difficulty of clinically recognizing topical TSA
2. The absence of widely available patch testing to diagnose TSA
3. The unpredictable cross-reactivity of steroid molecules
4. The variability of topical steroid vehicle formulations

The Exceptional Difficulty of Clinically Recognizing Topical Steroid Allergy

Probably the most significant reason why TSA is under-recognized is that it has no "typical" presentation. It should be considered in *all* patients who either do not respond as expected to topical steroids or who get worse on topical steroids.[3,4] Even more suspicious are patients who have a long history of dermatitis and steroid use and those who have used a steroid with a good response but then deteriorate, either flaring while still on the steroid or flaring once it has been discontinued.[3,4]

Such patients, of course, are often encountered in clinical practice. Four examples follow. The resolution of each case is presented at the end of this article. For which cases should TSA be considered and, for those cases, how likely is it?

Patient 1: A middle-aged female presented with persistent eyelid dermatitis (Figure 1). This had been present for several months, and she had been seen by multiple dermatologists. Over the years, she had made many changes in personal care products and cosmetics.

Patient 2: An elderly male presented with scalp pruritus. The scalp had been itching for months and revealed mild erythema and scaling. Seborrheic dermatitis was diagnosed and clobetasol foam was prescribed. The patient returned two months later with worsening scalp pruritus and the onset of new vesicular hand dermatitis (Figure 2).

Patient 3: A college-aged female presented with a flare of her atopic dermatitis while in college (Figure 3). Her atopic dermatitis had started in early childhood and had been well controlled with mometasone furoate ointment for many years. Several topical steroids had been prescribed without benefit since the advent of the flare.

Patient 4: A middle-aged female presented with a long-standing dermatitis of the lower legs (Figure 4). She had been treated with compression therapy and many different topical steroid ointments without benefit.

The Absence of Widely Available Patch Testing to Diagnose Topical Steroid Allergy

One reason that TSA has been under-recognized is that patch testing to steroid molecules and to propylene glycol (the most common vehicle allergen) has not been widely available. For a disease with no typical clinical presentation, like TSA, the absence of a diagnostic test means that the diagnosis cannot be made. An analogy would be trying to diagnose prodromal bullous pemphigoid if immunoflourescence was not available.

It has been suggested that patch testing with tixocortol pivalate and budesonide will diagnose 90% of patients who are allergic to active steroid molecules.[5,6] Patch testing to these agents was, until recently, only available by performing comprehensive patch testing, which was available in less than 30% of dermatology offices.[7] Fortunately, these two allergens were recently added to the Thin-layer Rapid Use Epicutaneous Test (T.R.U.E.TEST®) (Smart Practice, Phoenix, AZ), which should facilitate the diagnosis of TSA.

However, it is extremely important to remember that allergy to components of topical steroid vehicles, especially propylene glycol, probably cause TSA as frequently as allergy to the actual steroid molecules. Propylene glycol is a very common allergen, with the highest known prevalence of contact allergy, as it has been shown that 2.9% of patch-tested pa-

FIGURE 1. Eyelid dermatitis in a middle-aged female.

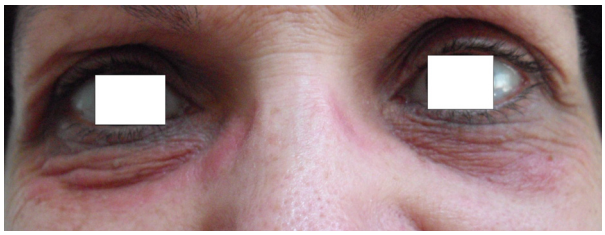


FIGURE 2. Vesicular hand dermatitis in an elderly male.

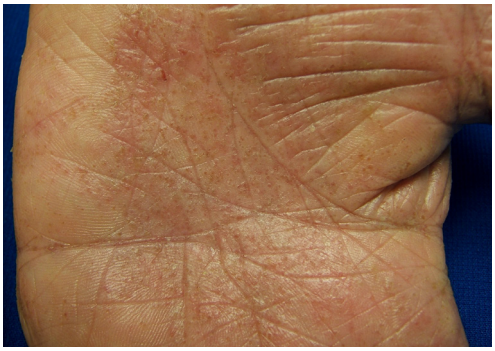
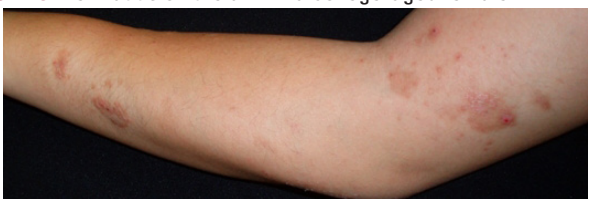


FIGURE 3. Dermatitis on the arm in a college-aged female.



tients react to it.[1] Propylene glycol is not included in the allergens tested by the T.R.U.E. TEST. However, additional vehicle allergens commonly used in topical steroids that are assessed by the T.R.U.E. TEST include parabens, lanolin, formaldehyde-releasing preservatives, and methylchloroisothiazolinone/methylisothiazolinone.

The Unpredictable Cross-reactivity of Steroid Molecules

The corticosteroid molecules evaluated by patch testing have been separated into five groups based on structure and cross-reactivity patterns, and they are designated A, B, C, D1, and D2.[8,9] From a structural perspective, the key sites are carbon 16 and 17 on the D ring of the corticosteroid molecule (Figure 5).

Class A: No modifications on C16 or C17 of the D ring
Class B: C16 and C17 have a -cis, -diol, or -ketal ring structure
Class C: C16 methyl group, no esters on C17
Class D1: C16 methyl group, ester on C17
Class D2: No methyl group on C16, ester on C17

Steroids in a given group have a high likelihood of cross-reacting with each other and there is frequent cross-reactivity between Class A and Class D2, as well as between Class B and Class D2.[10] However, it has become clear that many patients with corticosteroid allergy do not follow the predicted cross-reactivity patterns: patients have unexpectedly broad intergroup cross-reactivity (allergy to many steroids in different cross-reactivity groups) and others have unexpectedly narrow intragroup cross-reactivity (allergy to only one or a few steroids but not to others in the same group).[4]

FIGURE 4. Dermatitis on the lower leg in a middle-aged female.

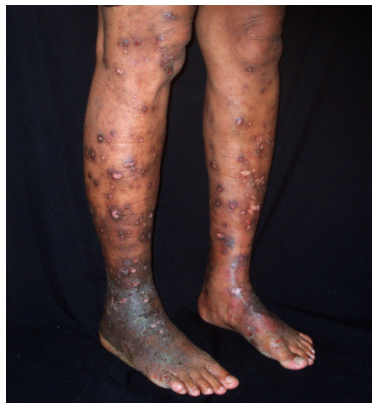
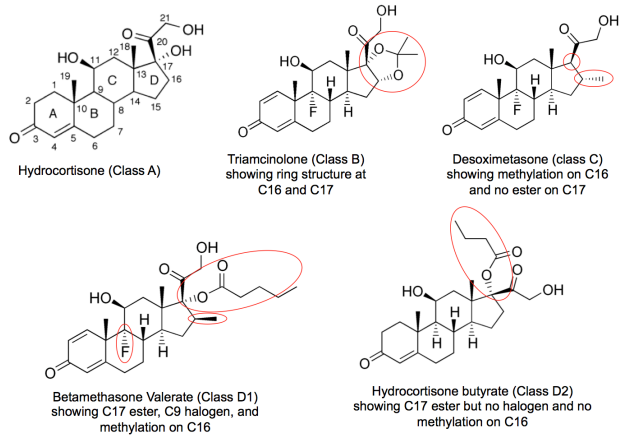


FIGURE 5. Structures of representative steroid molecules from each allergen class.



This unpredictable cross-reactivity means that even the astute clinician who does suspect TSA may be misled unless comprehensive patch testing is performed. First, if TSA is suspected and the patient is switched to a steroid of a different allergenicity group, the patient may not improve if they have broad intergroup cross reactivity. Alternatively, a patient with narrow intragroup cross-reactivity may improve when switched from one steroid in a group to another steroid in the same group, leading the clinician to mistakenly assume they did not have TSA.

The Variability of Topical Steroid Vehicle Formulations

Traditionally it has been taught that allergy to ointment vehicles is rare, but this is not true because both creams and ointments commonly contain allergens, especially propylene glycol.[11] In fact, based on the most recent published data regarding the most commonly prescribed branded and generic topical steroids, the respective percentages of steroid gels, steroid creams, steroid ointments, and steroid solutions containing propylene glycol are 91%, 71%, 58%, and 48%.

Even more challenging is the concept that when a generic prescription is written the vehicle may change from one refill to the next, leading to flares and remissions that the clinician is unable to relate to the vehicle. For example, if the prescription for generic triamcinolone

cream is written, it may be filled with a product from manufacturer X, whose cream vehicle contains propylene glycol. If the patient is allergic to propylene glycol, they either may not get better or may get worse. If they get the prescription refilled, even at the same pharmacy, it may be refilled with a product from manufacturer Y, whose cream vehicle does not contain propylene glycol, in which case they will improve. The next refill may subsequently be with another propylene glycol containing cream, leading to another deterioration.

Recommendations

Topical steroid allergy is common. There is no question that clinicians should have a high index of suspicion for TSA, especially in patients whose dermatitis does not improve with a topical steroid, who get worse on a topical steroid, or who have a chronic dermatitis.

The astute clinician has three possible approaches to managing TSA. Two of these approaches are reactive, managing the problem only after the clinician suspects TSA. The third approach is proactive, with the clinician attempting to prevent patients from developing TSA in the first place.

The first reactive approach is to initially prescribe topical steroids without considering the possibility of TSA allergy. If a patient does not get better, gets worse, gets better initially but then deteriorates while on the steroid, or gets better on the steroid but then flares when it is discontinued, TSA is *reactively* considered after the patient potentially experiences an adverse event. At this point, the patient is referred for comprehensive patch testing (use of the T.R.U.E. TEST is not sufficient, as it will miss allergy to propylene glycol in vehicles and allergy to some topical steroid molecules).

The second reactive approach starts, again, with initially prescribing topical steroids without considering the possibility of TSA allergy. If the patient has any of the courses noted in the previous paragraph, TSA is again *reactively* considered after the patient has already potentially experienced an adverse reaction. In this approach, though, instead of referring the patient for comprehensive patch testing, the clinician prescribes a class C steroid that does not contain any vehicle allergens. The only steroids available in the United States that meet this criteria are desoximetasone 0.25% ointment (Class 2 potency), desoximetasone 0.05% ointment (Class 4 potency), and desoximetasone 0.05% gel (class 2 potency), all of which are available as generic products.

The proactive approach is to initially prescribe topical steroids with the intent to avoid TSA. The goal in this approach is to avoid unnecessarily placing patients at risk for an adverse event. In this approach, class C steroids without vehicle allergens are prescribed as first-line agents in all instances in which there is a clinically appropriate product available. If there is no such product available, then either a class C steroid in a cream vehicle or a class D1 steroid in either an ointment or solution vehicle is prescribed, as these products have the lowest risk of allergenicity.

Case Resolutions

Patient 1: This patient had been prescribed desonide ointment by one of the first dermatologists she saw. Because the onset of the dermatitis preceded the desonide prescription, it had not been considered as a possible etiology. Patch testing revealed an allergy to class B steroids, which include desonide. 0.05% desoximetasone ointment was prescribed, the eyelid dermatitis resolved, and the steroid was able to be discontinued. The etiology of the original eyelid dermatitis was suspected to be irritant dermatitis that was then exacerbated by TSA.

Patient 2: Patch testing revealed an allergy to propylene glycol, which was present in the clobetasol foam. Replacement with a propylene glycol free class D steroid solution resulted in resolution of the vesicular hand dermatitis and improvement in the scalp pruritus. The final diagnosis was seborrheic scalp dermatitis complicated by TSA.

Patient 3: Patch testing revealed an allergy to class B and class D steroids, which included all preparations the patient had been prescribed. 0.25% desoximetasone ointment was prescribed, and she improved rapidly. The final diagnosis was atopic dermatitis complicated by TSA.

Patient 4: Patch testing revealed allergy to propylene glycol, which was present in most of the topical steroids the patient had been prescribed. 0.25% desoximetasone steroid ointment was prescribed, propylene glycol avoidance was instituted, and she dramatically improved. The final diagnosis was stasis dermatitis complicated by TSA.

DISCLOSURES

Matthew Zirwas MD has served as a paid consultant for Valeant, Taro, Onset, and SmartPractice.

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