CORTICOSTEROIDS AND CONTACT DERMATITIS

This article focuses on the epidemiology, pathophysiology, and clinical manifestations of topical and systemic corticosteroid- induced contact dermatitis.

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Allergic contact dermatitis (ACD) affects more than 14.5 million Americans each year, notably defining itself as an important widespread disease.[1] Due to overwhelming patient morbidity, loss of school and work time, and significant expenditures for health care visits and medicaments, ACD presents with a high economic burden. Fortunately, through keen patient interviewing and patch testing, a culprit may be identified. Therefore, remission can occur with implementation of an allergen avoidance regimen.

Education becomes the critical bridging intervention to ensure treatment adherence and symptom resolution. Patients who are unable to comply with avoidance regimens are at risk for sustained, recurrent, progressive, or even systemic dermatitis.[2,3] To ensure patients have an appropriate understanding of all the potential outcomes and their central role in disease pathology and treatment, education of the patient may occur even before the diagnostic patch test is placed.

Important aspects of patient counseling include explaining the nature of their disease, for example, the delayed presentation of ACD [aka the importance of a delayed read at 96 hours]; the relationship with the immune system (sensitization to a chemical followed by elicitation of dermatitis with re-exposure); and, the indifference to time (a substance the patient has been using regularly, briefly, or intermittently can sensitize at any point.) In certain cases, the topics of irritant contact dermatitis (ICD) and contact urticarial (CU) are also explained. Of note, unlike ACD, history rather than patch testing can often lead one to the correct diagnosis of ICD and CU.

ICD, the most prevalent form of contact dermatitis, can at times precede or be a concomitant diagnosis with ACD.[4,5] Unlike ACD, ICD may occur on the first exposure to an irritating or abrasive substance. The innate immune system is activated and inflammation ensues. CU (wheal and flare reaction), on the other hand, represents the least prevalent form of the contact dermatitis. It is an immune-mediated phenomenon governed by a hallmark IgE and mast cell-mediated immediate-type hypersensitivity reaction. We acknowledge this form of hypersensitivity due to its potentially deadly anaphylactic reactions and direct the reader to key sources.[6-8]

This article focuses on the role of topical and systemic corticosteroids within contact dermatitis and explores the epidemiology, pathophysiology, and clinical manifestations of such interactions.

HISTORICAL PERSPECTIVE

In the early 20th century, the adrenal gland became the focus of medical research after the discovery of the lifesaving potential of adrenalin. Enthused by the idea of an undiscovered frontier of adrenal gland products, Edward Calvin Kendall worked endlessly to isolate several hormones from the adrenals, including cortisone and hydrocortisone. By joining forces with the military and Merck pharmaceuticals,' researcher Lewis Sarett produced the first synthesized cortisone from ox bile at a cost of $200/g.[9] Dr. Kendall was ultimately co-awarded a Nobel Prize in Physiology or Medicine (c. 1950) for his contribution to cortisone discovery.

Topical hydrocortisone became available in the 1950s. The first reported dermatologic use came from Drs. Spies and Stone from Alabama—they successfully treated chronic hand dermatitis.[10] Nevertheless, the treatments remained expensive until the Syntex Company discovered a way to use sarsasapogenin, a plant steroid from Mexican yams, to produce a $6/g cortisone.[11]

ACD AND TOPICAL CORTICOSTEROIDS

Epidemiology

As corticosteroids became the primary treatments for cutaneous inflammatory conditions, including ACD, so did the cases of corticosteroid-induced ACD begin to emerge with the first 2 cases reported in 1959.[12,13] However, it was not until the 1990s that the North American Contact Dermatitis Group added the class A and B corticosteroids to their North American Standard Series of patch tests. Corticosteroids were ultimately deemed as "Allergen of the Year" in 2005.[14]

The current reported prevalence of topical corticosteroid-induced ACD ranges from 0.2% to 6%.[15] A Danish retrospective study of 3594 patch-tested patients found that the overall frequency of any topical corticosteroid allergy to be 2%, specifically 0.8% had tixocortol-21-pivalate specific allergy, 1% had budesonide specific allergy, and 1% had hydrocortisone-17-butyrate.[16] A Mayo Clinic-based retrospective study of 1188 patch-tested adults found that 10.7% of participants had a prevalent positive reaction to at least 1 topical corticosteroid, and 4.7% had a prevalence of reactions to multiple.[15]

The prevalence results are variable because of differences in patch test application and interpretation. Generally, tixocortol-21-pivalate (tixocortol pivalate) is used as the primary screening agent for groupA corticosteroids, which includes hydrocortisone and prednisone. Shaw and Maibach[17] assessed the clinical relevance of positive patch test reactions to tixocortol via the repeated open application test (ROAT). Their results showed that 75% of patch-test positive patients had concurrent positive ROAT to hydrocortisone cream, and 38% had positive ROAT to hydrocortisone ointment. The difference in ROAT positivity was attributed to the vehicles' differing transepidermal penetrations.

Pathophysiology

The allergenic potential of corticosteroids is multifactorial. The factors that make corticosteroids preferred treatments for acute inflammation also serve to enhance their allergenicity. As a steroid, cortisol is extremely lipophilic and has a low molecular weight allowing it to easily slip through the cell membrane. At this stage, it is too small to induce an immune response. However, within the aqueous cell environment, cortisol is degraded into a steroid glyoxal via the loss of C21, which, when combined with serum or skin proteins, becomes an allergen and can induce hypersensitivity.[18] This degradation is facilitated better in an alkaline environment which is found in areas more prone to sweat (axilla, perineum), and in diseased skin such as that affected by atopic dermatitis, venous stasis, or bacterial infections.[19]

As discussed earlier, ACD comprises a delayed-type IV allergic reaction. However, the specific role of T cells continues to be investigated. Generally, cytotoxic CD8 T cells are found in severe bullous reactions such as toxic epidermal necrolysis, whereas CD4 T helper cells are present in nonbullous reactions, with the Th1 and Th17 cells predominating in allergic pathogenesis[20] and Th2 response reported occurring only on exception.[21]

However, there is mounting evidence that CD8 T cells play a prominent role in ACD.[22,23] Baeck et al[24] analyzed the T cell recruitment and cytokine production profile in 27 patients with positive patch tests to corticosteroids as compared to nonsensitized controls. They found that a CD3+ T cell response predominated with a Th2 cytokine profile (interleukin [IL]-4, IL-5). Interestingly, a CD8 T cell predominance was absent in the corticosteroid-sensitive patients. Thus, the T cell mechanisms behind corticosteroid-induced ACD need continued research to be fully elucidated.

ACD AND NON-CUTANEOUS CORTICOSTEROIDS

Rarely, immediate-type hypersensitivity reactions can occur after topical, oral, or parental administration of corticosteroids.[25] The first such reactions were reported in the 1950s by Kendall[26] in patients receiving numerous corticosteroid injections. The incidence of anaphylaxis following intravenous corticosteroids in children has been reported at 0.5%.[27] These reactions are mediated by an acute IgE-mediated hypersensitivity, rather than the T cell dominant delayed response.

RE-CLASSIFICATION OF CORTICOSTEROIDS

Topical corticosteroids have traditionally been classified by their molecular configuration. In 1989, Coopman et al[28] defined 4 classes of topical steroids titled A (hydrocortisone type), B (triamcinolone acetonide type), C (betamethasone type), and D (clobetasone or hydrocortisone esterified types). This classification expanded to include subdivided classes of D1 (betamethasone dipropionate type) and D2 (methylprednisolone aceponate type).[29] This subdivision was clinically significant because the D2 group was found to be highly cross-reactive with group A and budesonide.[30]

In 2011, a new simplified classification was developed by Baeck et al.[31] This system includes 3 separate groups subdivided on the basis of allergic potential. Group 1 includes nonmethylated compounds including those in Group A, D2, and budesonide—these are responsible for the majority of allergic reactions; Group 2 contains halogenated molecules with C16/C17 cis ketal/diol structure and include the previously designated Group B structures; and Group 3 includes halogenated and C16-methylated molecules previously found in groups C and D1, these have the least allergic potential (**Table**)[31,32]

PRACTICALS OF PATCH TESTING

Patch testing is often necessary to identify the relevant allergen(s) responsible for the patients' ACD. Screening patch test trays are available to isolate the most common chemicals and offer the provider clues for potential sources. The American Contact Dermatitis Society (ACDS) North American Standard Series includes allergens from several different categories.[33] Supplemental trays (such as hairdressing, dental materials, cosmetics, and fragrance/flavors) are also available for purchase.[34,35]

Furthermore, some personal products can be tested "as is", for example the European Cosmetics Toiletry and Perfumery Association advises hair dye manufactures to instruct consumers to perform a self-allergy test prior to product use; however, instructions often vary even among products from

Table. CORTICOSTEROID CLASSIFICATIONS BASED ON ALLERGENCITY[31,32]

Group 1 (Previously A, D2, and Budesonide)	Group 2 (Previously B)	Group 3 (C, D1)
Budesonide	Amcinonide	Alclomethasone dipropionate
Cortisone acetate	Desonide	Beclomethasone dipropionate
Fludrocortisone acetate	Flunisolide	Betamethasone
Fluprednisolone acetate	Fluocinolone acetonide	Betamethasone 17-valerate
Hydrocortisone	Fluocinonide	Betamethasone dipropionate
Hydrocortisone aceponate	Halcinonide	Betamethasone sodium phosphate
Hydrocortisone acetate	Triamcinolone acetonide	Clobetasol propionate
Hydrocortisone 17-butyrate	Triamcinolone diacetate	Clobetasol butyrate
Hydrocortisone 21-butyrate	Triamcinolone hexacetonide	Dexamethasone
Hydrocortisone hemisuccinate		Dexamethasone acetate
Isoflupredone acetate		Dexamethasone sodium phosphate
Methylprednisolone aceponate		Diflucortolone valerate
Methylprednisolone acetate		Diflucortolone diacetate
Methylprednisolone hemisuccinate		Flumethasone pivalate
Prednisolone		Fluticasone propionate
Prednisolone pivalate		Mometasone furoate
Prednisolone succinate		
Prednisone		
Tixocortol pivalate		
Triamcinolone		

the same company, and it is unclear how many consumers of the intended audience actually follow through with the process.[36]

PEARLS OF TREATMENT: EVERY DOSE COUNTS IN AVOIDANCE

A person may be exposed to, and subsequently sensitized to a particular allergen for days to years before actually developing ACD. Exposures can be additive, eventually causing one's immune system to become trained to identify a chemical, at which time a cutaneous response would be elicited upon exposure.[4] From a pathophysiologic standpoint it is logical that the repeated contact over time which lead to immune stimulation and hypersensitivity, conversely translates to repeated avoidance over time inducing remission. Avoidance creativity, however, may be necessary by utilizing alternatives and being aware of indirect exposures.

There are programs available to aid in the avoidance endeavor. The Contact Allergen Management Program, a service offered through ACDS, and the Contact Allergen Replacement Database, developed by Mayo Clinic, can assist with identifying allergen-free products.[37,38] Both programs allow the provider to personalize "shopping lists" of products void of specific dermatitis-inducing chemicals, as well as any cross-reactors. ■

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Additional references at www.the-dermatologist.com.