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CASE REPORT

Acute Urticaria Induced by Systemic Corticosteroids in Patient with Pre-existing Aspirin Exacerbated Respiratory Disease

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INTRODUCTION

Despite the allergic, inflammatory, and immunologic modulating properties of corticosteroids, acute and delayed hypersensitivity reactions have been reported.[1-9] There is increasing data regarding hypersensitivity reactions to systemic corticosteroids from these reports. The prevalence of hypersensitivity reactions with topical corticosteroids is 2.9 - 6%[10-12] and less than 1% with inhaled and systemic corticosteroids.[1,2,13]

Delayed hypersensitivity reactions after topical corticosteroid use have been reported for decades and they were recognized as the allergen of the year in 2005 by the American Contact Dermatitis Society.[14] Acute IgE-mediated hypersensitivity reactions occurring within one hour are characterized by urticaria and anaphylaxis; while delayed T-cell mediated reactions are characterized by urticaria and maculopapular exanthems.[14,15] Reactions may occur to the corticosteroid or to its allergens, making it difficult to identify the true culprit.[15]

We identified a patient without pre-existing urticaria who exhibited hypersensitivity reactions to oral steroids (prednisone and methylprednisolone), inhaled corticosteroids/long-acting beta agonists (fluticasone/salmeterol and budesonide/formoterol), and aspirin which caused acute urticaria, angioedema, and bronchospasm. Clinicians, particularly emergency room staff, must be aware of the potential for hypersensitivity to corticosteroids and consider it in the differential diagnosis of a patient who has received corticosteroids with subsequent sequelae of a hypersensitivity reaction.

CASE REPORT

The patient was a 58-year-old female with a history of allergic rhinitis, classic aspirin exacerbated respiratory disease (AERD), and drug-induced urticaria for almost three decades. Her first prednisone exposure was thirty years prior for an asthma exacerbation. Within 12 hours, she developed urticaria and has not used oral steroids since. In 2012, she was given methylprednisolone for asthma and developed urticaria within 12 hours after the initial dose (Figure 1). She was challenged with prednisone 60 mg, and a similar reaction was observed. Additionally, she had developed urticaria within several hours of using fluticasone/salmeterol and budesonide/formoterol. Interestingly, she has tolerated inhaled fluticasone, intranasal fluticasone, and inhaled beta agonists alone, making the etiology of this reaction difficult to determine.

As the patient had AERD, we attempted aspirin desensitization, but she developed mild urticaria prior to desensitization with a pretreatment protocol of prednisone. The patient was brought back for aspirin desensitization without prednisone, and over the next six hours had progressive urticaria associated with difficulty breathing. Thus, the desensitization was discontinued. Her tryptase level was normal. Given her recurrent immediate and delayed hypersensitivity reactions to systemic and inhaled corticosteroids, further diagnostic testing was pursued.

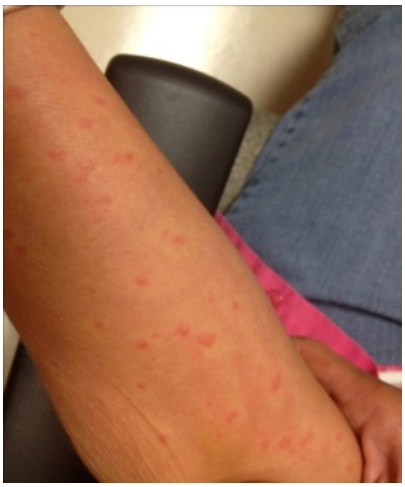

Figure 1. Acute urticaria appeared within 12 hours after taking oral prednisone.

Skin testing. We used the following medications for testing: prednisolone sodium phosphate oral solution 3 mg/1 ml (Morton Grove Pharmaceuticals, IL), dexamethasone sodium phosphate injection suspension 4 mg/1 ml (APP Pharmaceuticals, LLC, Schaumburg), methylprednisolone acetate injection suspension 40 mg/1 ml (Novaplus, USA), and saline negative control and histamine positive control.

Skin puncture tests (SPT; Table 1) were performed with each of the corticosteroids in 10-fold increasing concentrations (1:100, 1:10, to undiluted). A wheal ≥ 3 mm larger than the negative control (saline) was considered positive. Tests were read at 20 minutes. Intradermal tests (Table 2) with the same corticosteroids were performed in 10-fold increasing concentrations (1:100 to 1:10) only if the SPTs were negative. Skin puncture tests (SPT; Table 1) were performed with each of the corticosteroids in 10-fold increasing concentrations (1:100, 1:10, to undiluted). A wheal ≥ 3 mm larger than the negative control (saline) was considered positive. Tests were read at 20 minutes.

Intradermal tests (Table 2) with the same corticosteroids were performed in 10-fold increasing concentrations (1:100 to 1:10) only if the SPTs were negative. One volunteer who was known to tolerate corticosteroids was used as a control. His skin testing was negative with adequate positive and negative controls, verifying these were non-irritating concentrations of steroid.

By traditional skin testing, she was positive to all steroids and should avoid systemic steroids. It was also determined that she would not be able to tolerate aspirin desensitization with corticosteroid premedication.

Table 1. Skin puncture test results.

REAGENT	WHEAL/FLARE (mm)	RESULTS
Percutaneous testing		
Saline	0/0	Negative
Histamine	5/5	**Positive**
Prednisolone 3 mg/ml (1:100)	0/0	Negative
Methylprednisolone 40 mg/ml (1:100)	2/2	Negative
Dexamethasone 4 mg/ml (1:100)	0/0	Negative
Prednisolone 3 mg/ml (1:10)	0/0	Negative
Methylprednisolone 40 mg/ml (1:10)	0/0	Negative
Dexamethasone 4 mg/ml (1:10)	2/2	Negative
Prednisolone 3 mg/ml	0/0	Negative
Methylprednisolone 40 mg/ml	4/4	**Positive**
Dexamethasone 4 mg/ml	4/6	**Positive**

Table 2. Intradermal test results.

REAGENT	WHEAL/FLARE (mm)	RESULTS
	Zero time	20 minutes after
Saline	7/0	Negative
Prednisolone 0.03 mg/1 ml (1:100)	5/0	4/0 Negative
Methylprednisolone 0.4 mg/1 ml (1:100)	5/0	6/9 Negative
Dexamethasone 0.04 mg/1 ml (1:100)	5/0	7/0 Negative
Orapred 0.03 mg/1 ml (1:10)	6/0	10/0 **Positive**

DISCUSSION

Corticosteroids often are referred to as "steroids" and are produced synthetically. They are related closely to cortisol, a hormone naturally produced from cholesterol within the adrenal cortex (Figure 2). Corticosteroids have been used since the late 1940s for their anti-inflammatory and immunomodulatory effects to treat a wide variety of diseases.[16] Despite their clinical efficacy, steroids can induce multiple severe adverse effects, including hypersensitivity reactions, weight gain, agitation, and skin thinning, limiting their long-term use.[17]

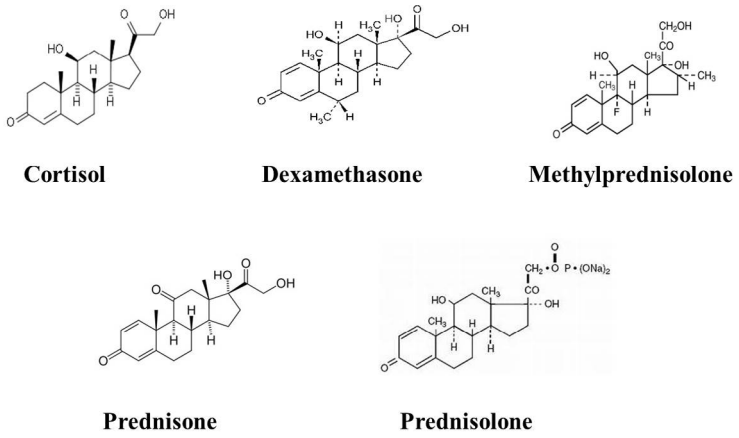

Figure 2. Structural formulas of different steroids.[4,7,18]

The overall rate of hypersensitivity reactions to corticosteroids appears to be low in comparison with their high utilization.[17] However, these reactions may be under-diagnosed; especially in cases where corticosteroids are being used to treat an ongoing allergic reaction and the reaction to the corticosteroid may confound the clinical picture. Risk factors that have been described for hypersensitivity reactions to corticosteroids include atopy, contact dermatitis, drug allergy, asthma or renal transplant. However, it is not clear if these are truly risk factors or represent conditions in which corticosteroid use is prevalent and therefore, a higher number of patients have hypersensitivity reactions.[17] The corticosteroids most frequently implicated in hypersensitivity reactions are non-fluorinated, such as topical hydrocortisone and budesonide and systemic methylprednisolone and hydrocortisone.[1,18] In a few cases, the reactions can be induced by salts, such as succinate, or rarely by diluents such as carboxymethylcellulose or metabisulfite.[3-5,19] With topical corticosteroids, the reaction can be due to other ingredients, such as neomycin or cetyl stearyl alcohol.[19]

Some authors only found skin test positivity with the topical corticosteroid,[3,4,19] while others[20] showed that the corticosteroid was responsible for the reaction in a patient who developed bronchospasm after intravenous methylprednisolone. The majority of hypersensitivity reactions to corticosteroids appear to be due to Gell and Coombs Type I and Type IV immunologically mediated mechanisms.[1-3,6-8,20] Type I (acute) reactions classically occur less than one hour after drug administration, are mediated by drug-specific IgE antibodies, and typically present with urticaria and anaphylaxis. Type IV (delayed) reactions are induced by T cells, occur within an interval of twenty-four to forty-eight hours, and commonly present with urticaria and maculopapular exanthems.[2,9,19,20] Our patient had evidence of an IgE mediated reaction based on the results of the skin testing, utilized for acute hypersensitivity reactions.

Assessment of cross-reactivity to corticosteroids may be difficult as most individuals have received corticosteroids either topically or systemically at some point in the past.

In many cases, patients do not remember receiving the corticosteroid, nor do they recall the type of corticosteroid they received. In those cases, it is difficult to confirm whether the clinical presentation is due to cross-reactivity or prior sensitization.

CONCLUSION

Hypersensitivity to corticosteroids is recognized more in the literature.[1,2,19,20] Corticosteroid reactions have important therapeutic consequences, given the frequency they are used in the treatment of a myriad of disease processes.[1,2,19-21] Although rare, allergic reactions to corticosteroids exist and an immunological mechanism, IgE or T cell dependent, have been established.[20,21] Skin testing, in-vitro testing, patch testing, and drug provocation tests are useful diagnostic tools to determine sensitivity. Patients who notice a new rash or worsening of their skin disease after using corticosteroids should alert their physicians, who should be aware to the possibility of a hypersensitivity reaction. Emergency room staff, in particular, must be aware of corticosteroid hypersensitivity reactions and take this into consideration in a patient who has received corticosteroids.

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