
Review article

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Corticosteroid-induced hypersensitivity reactions

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Objective: To review and present data on the prevalence, clinical manifestations, diagnostic techniques, and management options in patients with hypersensitivity reactions to corticosteroid preparations.

Data Sources: All English language articles pertaining to human subjects were reviewed using the Pubmed database from 1964 to June 2002. Indexing terms used were anaphylaxis OR allergic OR anaphylactoid OR hypersensitivity AND steroid OR corticosteroid. Further cross-references were obtained after reviewing articles from the aforementioned search.

Study Selection: A total of 11,493 articles were identified with the above search terms. Only those articles, including letters and editorials, describing systemic reactions to steroids were included in the review. Excluded from our review were articles dealing with contact dermatitis to topical steroid preparations. This resulted in a total of 80 articles which were reviewed.

Results: Although rare, steroid-induced hypersensitivity reactions do occur. They range from minor rashes to the more serious cardiovascular collapse. The mechanisms of steroid-induced adverse events vary from patient to patient, some being classic immunoglobulin E-mediated whereas others are pseudoallergic in nature. Skin testing and provocative challenges offer two ways to diagnose such reactions. Treatment consists of substituting the steroid with an alternative preparation which can be tolerated by the patient.

Conclusions: Although little is known about the epidemiology of steroid-induced hypersensitivity, because most data are derived from case reports, it is clear that steroid-induced hypersensitivity is a heterogeneous entity, with no single uniform mechanism. A great deal of work still needs to be done so that the pathogenesis of such adverse events can be clearly determined and effective therapeutic interventions devised.

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INTRODUCTION

Case Vignette

A 19-year-old woman with systemic lupus erythematosus (SLE) was admitted to our hospital with hypertensive encephalopathy. She had been diagnosed with SLE at the age of 11 years when she presented with arthralgias, facial rash, and alopecia along with strongly positive antibody titers for antinuclear antibody and anti—double-stranded DNA. She responded well to treatment with daily oral prednisolone with a slow taper. Three years later she developed lupus glomerulonephritis and nephrotic syndrome for which she received three doses of high-dose intravenous (IV) methylprednisolone (MP) sodium succinate (Solu-Medrol, Pharmacia & Upjohn, Kalamazoo, MI), without any untoward incident, and was also started on oral cyclophosphamide. Over the next several years, she was admitted multiple times for lupus flares, most of which were precipitated by abrupt discontinuation of her medications because of noncompliance; each flare responded to three to five doses (30 mg/kg/dose) of IV Solu-Medrol.

During her most recent hospitalization for hypertensive encephalopathy, she was found to be in an acute nephritic flare and admitted to stopping all her medications. Once again, she was treated with high-dose IV Solu-Medrol (three doses) and also started on oral tacrolimus. She was then discharged with instructions to continue on a regimen of alternate-day oral prednisolone, oral tacrolimus, and a tapering schedule of IV Solu-Medrol infusions. At the time of her first outpatient infusion, the patient developed a pruritic papular erythematous rash on her face, neck, and bilateral anterior arms immediately after the start of the infusion. This was not associated with respiratory distress or hypotension. The infusion was immediately stopped and IV diphenhydramine was administered. This resulted in the resolution of all her symptoms within a period of 2 hours. The patient had a similar reaction to a subsequent dose of IV Solu-Medrol, even though the IV Solu-Medrol preparation used this time was preservative-free. The patient was then referred for skin testing. Both intradermal and scratch tests were performed to a variety of corticosteroid preparations using histamine as the positive control and saline as the negative control. The patient had an immediate response (pruritic indurated erythematous lesion) to Solu-Medrol (both with and without benzyl alcohol) and to histamine, but she did not react to saline, or to other corticosteroid preparations (dexamethasone sodium phosphate and hydrocortisone sodium succinate).

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HISTORICAL BACKGROUND AND OVERVIEW

The discovery and clinical application of corticosteroids by Drs. Edward C. Kendall, Philip S. Hench, and Tadeus Reichstein in the mid-1930s have revolutionized the care of patients with a variety of immune-mediated disorders.^{1,2} Corticosteroids not only have a crucial role in the therapeutic and preventative management of patients with disorders such as severe asthma,³⁻⁵ idiopathic anaphylaxis,⁶ and atopic dermatitis,⁷ but they are also an integral part of standard immunosuppressive regimens for patients with autoimmune disorders such as SLE⁸ and for organ transplant recipients.^{9,10} Corticosteroids mediate their effects by suppressing the transcription of a variety of pro-inflammatory cytokines¹¹ by reversing the acetylation of histones, which is an important step in inflammatory gene transcription.¹² Other postulated mechanisms contributing to their immunosuppressive effects include apoptosis of basophils¹³ and inhibition of the expression of adhesion molecules on endothelial cells such as vascular cell adhesion molecule-1.¹⁴ Paradoxically, corticosteroids may also have a pro-inflammatory effect by suppressing the production of interleukin-12¹⁵ and interferon- γ ,¹⁶ the lack of which can be expected to polarize the T cell response toward the pro-inflammatory Th2 pattern. Another potentially curious effect of corticosteroids on the immune response is their stimulatory effect on interleukin-4 mediated immunoglobulin (Ig)E synthesis by B-lymphocytes, both *in vitro*¹⁷ and *in vivo*.¹⁸ However, whether these observations have any relevance to the development of steroid-induced allergic reactions is speculative at best. Although contact dermatitis from topical corticosteroids is quite commonly reported in the dermatologic literature,¹⁹ reports of systemic allergic reactions to steroid preparations are rare, considering the frequency of steroid use. Several reports documenting hypersensitivity reactions to almost all types of corticosteroid preparations can be found in the medical literature. Kendall²⁰ noted untoward effects related to the use of hydrocortisone as far back as 1958. Eleven patients treated by him with intra-articular hydrocortisone developed localized urticaria, 8 had generalized urticaria, and 1 developed angioedema and bronchospasm. At that time, these reactions were attributed to the various additives used in steroid preparations.

The first systematic study investigating the precise component of steroid preparations responsible for hypersensitivity reactions is attributed to Mendelson et al.²¹ Their report details the results of intradermal testing and provocative challenge with a variety of different steroid preparations and strengths in a 17-year-old adolescent with status asthmaticus who had developed an urticarial rash and exacerbation of his asthma soon after receiving two different IV steroid preparations (Solu-Medrol and Solu-Cortef, Pharmacia & Upjohn). Although intradermal testing with the two agents suspected of being responsible for the reactions was negative, surprisingly, an IV challenge with either agent at high doses elicited a bronchospastic and urticarial response. This report also raised questions regarding the utility of skin testing in the investigation of patients with suspected steroid hypersensitivity.

Since these early reports, there have been numerous case reports and letters describing patients with similar reactions to almost all types of steroids.

EPIDEMIOLOGY

Little is known about the exact prevalence of corticosteroid-induced hypersensitivity reactions in the general population, except that they are probably uncommon. This is understandable as most of our data on this subject come from anecdotal case reports. Having said that, it should also be recognized that many patients with adverse reactions to steroids probably do not get reported in the medical literature. Certainly, it is also plausible that several patients with steroid hypersensitivity are not recognized as having that, because the diseases that these patients are being treated with steroids for, may themselves manifest in ways that could mimic an allergic reaction to the drug (eg, bronchospasm in patients with asthma, and angioedema in patients with idiopathic anaphylaxis). Compounding these issues is the lack of well accepted consensus criteria for establishing whether reactions to administered medications are truly allergic in nature, and, with a few exceptions that will be mentioned later, the paucity of detailed immunologic investigations in such patients.

Nevertheless, at least one prospective study involving 213 children with rheumatologic conditions treated with IV steroids at a tertiary care center seems to support the notion that such reactions are, indeed, uncommon.²² Only 46 (22%) of the treated children reported an adverse event; almost half of them had to stop use of the medication because of the impact of the noted event. However, the majority of the reported events were behavioral (47% of all reactions). For an estimated 10,000 doses of steroids administered to these 202 children, reactions that were felt to be of an allergic nature were seen in approximately 0.1% (pruritus in 9, hives in 5, and only 1 anaphylactoid event).

Host Factors

Are there specific host factors that could increase the risk of developing a hypersensitivity reaction to steroids? The aforementioned study found no statistically significant differences, with respect to the ethnicity or underlying disease, between the children that did develop adverse events compared with the rest of the group. Although the investigators did find that the children who had developed adverse events (including those that developed behavioral changes) had a statistically higher incidence of previous history of reactions to other drugs, when the data are reanalyzed by including only those children with allergic-type reactions and compared with the children without any adverse events, the two groups are similar in their incidence of previous drug intolerance. Other studies have also tried to address this issue to determine whether a history of atopy or aspirin allergy could increase one's predisposition to develop corticosteroid hypersensitivity. Dajani et al²³ studied 11 aspirin-sensitive asthmatic patients with IV hydrocortisone and found that three developed a drop in their forced expiratory volume in 1 second. How-

ever, the validity of any conclusion from this study is compromised by the fact that the investigators did not have a control group of non—aspirin-sensitive asthmatic patients who were similarly tested. Many other reports of corticosteroid hypersensitive patients do not have any data on previous adverse reactions to other drugs,^{24–26} whereas some others clearly deny any history of drug sensitivity in their patients.^{27,28} Similarly, the role of atopy as a predisposing factor is quite unclear. The relationship is made even less clear when one acknowledges that it is patients with atopic diseases such as asthma who are more likely to receive steroids and so may be subject to selection bias. Therefore, although steroid sensitivity maybe encountered by clinicians more often in patients with atopic conditions, current data do not support any specific host factors that may predispose patients to steroid hypersensitivity. On a related issue, there are no reliable prospective data to determine whether patients with certain specific diseases are more likely to manifest steroid sensitivity. Although some studies have suggested that patients with renal transplants are at higher risk of adverse reactions,^{29,30} this may again be attributable to the frequent use of steroids in this patient population. In support of this, the study by Klein-Gitelman and Pachman,²² although restricted to a rheumatologic patient population, found no effect of the underlying disease on the risk of adverse events to IV steroids. Further, anaphylactoid reactions to steroids have been reported in the neurology,³¹ otorhinolaryngology,³² and cardiology³³ literature in nonatopic individuals.

Factors Related to the Drug Used

Although the most common agents to which hypersensitivity has been reported are hydrocortisone and methylprednisolone,^{21,23–30,33} almost all types of steroid preparations have been implicated as causative agents in hypersensitivity reactions, including prednisolone,³⁴ oral prednisone,^{35,36} dexamethasone,³⁷ and triamcinolone.³⁸ The same observation holds true for the route of administration of the steroid preparation. Although a large percentage of the reports are related to IV drug administration, topical,³⁸ oral,^{35,39} and even intra-articular³⁴ methods of administration of steroids have been noted to cause hypersensitivity reactions.

One area of continued debate relates to the whether these reactions are attributable either to the steroid itself or its specific salt, or rather, to the diluent or preservative in the steroid preparation. Mendelson et al²¹ tried to answer this question by a series of elegant skin tests and provocation testing in their previously mentioned 17-year-old asthmatic patient. When challenged, this patient developed bronchospasm after receiving IV Solu-Medrol (containing MP sodium succinate and a diluent). The patient also reacted to a similar dose of IV MP sodium succinate (without the diluent), and also to pure oral MP, leading the investigators to conclude that the patient was allergic to the steroid itself, and not to the diluent or to the specific steroid salt. These investigators also noted that the patient did not develop any reaction to lower doses of any of the aforementioned agents, which raises the

issue of a dose-response relationship. Similarly, Comaish³⁴ and Clee et al⁴⁰ noted positive skin test results in their respective patients when they used pure steroid preparations without any diluent, once again making the role of the excipient suspect. In contrast, several other investigators have noted clinical reactions in their patients only with specific salts of steroids such as succinate, but not with others such as acetate,^{41–43} suggesting that perhaps the salt itself may modify the reactivity of the steroid preparation by unmasking or altering the immunogenicity of some epitopes. This might also explain the findings of Chapman et al,²⁵ Mansfield et al,⁴⁴ and Fulcher and Katelaris,⁴⁵ all of whom noted that their patients had a positive skin test to different steroid salts, but not to the pure steroid preparation. It is difficult to reconcile such seemingly contradictory observations among investigators, except perhaps if one considers steroid hypersensitivity to be a heterogeneous entity, with some patients having an adverse reaction to the steroid itself, whereas others being intolerant to the specific salt, or rarely even to the diluent/preservative such as carboxymethylcellulose⁴⁶ or metabisulfite.⁴⁷

CLINICAL FEATURES

Patients with hypersensitivity reactions to steroids can present with a variety of clinical signs and symptoms ranging from urticaria^{21,40,48} to sudden cardiovascular collapse and death.^{30,49,50} Some of the more common reported events include pruritic rashes,^{25,34} bronchospasm,^{21,24} and hypotension.^{24,29,41,42} Although several deaths have been linked to the use of high-dose IV steroids, the causal role of steroids in these fatalities continues to be a matter of debate. It is also controversial as to whether these reactions, even if truly related to steroid administration, are allergic or not, as will be discussed in more detail in a later section of this article. Animal studies have shown that when infused rapidly, IV MP may cause hemodynamic changes including a significant drop in mean aortic pressure and peripheral vascular resistance⁵¹; these changes presumably result from α -adrenergic blockade and a negative inotropic effect of the medication, rather than from an immune-mediated reaction.

Although the majority of patients reported as having steroid hypersensitivity have developed reactions within a few minutes after administration of the offending agent, some have been delayed for as long as a few hours, again calling into question the immunologic basis of these reactions. In an early report by Pippen,⁵² the patient almost immediately developed a systemic reaction which peaked at approximately 10 minutes after application of the steroid ointment. A similarly rapid onset of bronchospasm was noted by Mendelson et al.²¹ Most patients with delayed onset of reactions have manifested with localized reactions such as urticaria or other skin rashes, some of which have appeared as long as 24 to 48 hours after administration of the drug.^{34,53,54} Occasionally, reactions described as being anaphylactoid have also been delayed by several hours.^{48,55} Overall, most patients who have had delayed reactions tend to have less severe symptoms with spontaneous resolution as compared with the more life-threat-

ening immediate-onset reactions. And although there some reports of patients with SLE dying several hours after high-dose IV MP administration without developing any previous allergic manifestations, the autopsies have been too inconclusive to implicate the steroids as a contributing factor in their deaths.⁵⁶

MECHANISM OF ADVERSE EVENTS

One of the most unclear aspects of steroid-induced hypersensitivity reactions is whether the reactions are truly immune-mediated and therefore allergic. To understand the implications of these distinctions we need to understand the meaning of the terms allergic, pseudoallergic, and adverse drug reactions. Although there are no consensus criteria on how to define the above terms, some criteria that have been proposed as being helpful are as follows.⁵⁷ An adverse drug reaction is an undesirable or unintended effect produced by the drug and one that occurs at appropriate doses. These reactions can be predictable and dose-dependent, occurring in normal individuals (eg, drug toxicity), or unpredictable and dose-independent, more commonly seen in a genetically susceptible subpopulation. Unpredictable adverse drug reactions that have an immunologic basis are said to be allergic or hypersensitivity reactions, whereas those that have clinical features similar to allergic drug reactions but do not involve the immune system are said to be pseudoallergic. An anaphylactic reaction is an allergic reaction that is IgE mediated; a reaction that resembles an anaphylactic reaction but one that is not immune mediated, is then termed an anaphylactoid reaction.

Some characteristics of hypersensitivity reactions to drugs are as follows:

- 1) Allergic reactions are rare and occur only in a minority of treated persons.
- 2) The clinical manifestations can not be explained by the known pharmacologic actions of the drug.
- 3) Symptoms usually develop after at least 1 week of being treated with a drug, unless the person has had previous exposure to the said drug.
- 4) The reaction can be produced even with low doses of the drug or with other agents having a similar structure.
- 5) The symptoms are generally acknowledged to be of an allergic nature, eg, urticaria, angioedema, anaphylaxis.
- 6) Blood or tissue eosinophilia may be present.
- 7) Specific antibodies or T cells that react to the allergen can be identified.
- 8) The reaction usually spontaneously resolves within several days after the drug is discontinued.

Let us now look at the reported cases of steroid-induced drug reactions and see how well they fit into the category of hypersensitivity reactions. First, what favors an immune-mediated mechanism for steroid-induced reactions is the rarity of these reactions, especially considering how commonly steroids are used, and second, the nature of the clinical manifestations, such as urticaria and bronchospasm, which are common in allergic diseases. Similar to other drugs, steroids probably act as haptens, binding with other macro-

molecules to form large immunogenic complexes which may then trigger an immune response by the body.⁵⁷

However, many observations argue against an allergic basis, at least for every reported case. First, as mentioned earlier, most of the reported reactions have occurred within minutes to, occasionally, hours of drug exposure, even in patients who have never before been exposed to the drug.^{28,41} One could argue that these individuals may have been sensitized by previous exposure to cross-reacting antigens (eg, certain foods) in the environment. Second, several investigators have demonstrated a dose-response relationship on provocative testing,^{21,24} which may indicate that the reaction, rather than being immunologic in nature, is more likely to be an adverse drug reaction due to drug toxicity and attributable to the known pharmacologic action of the agent. Further, only a few investigators have found elevated IgE levels,²¹ and in only a single report²⁸ was a specific IgE-antibody directed against the drug detectable. However, having said that, the lack of these antibodies should not necessarily disprove an immunologic basis for these reactions as haptens would need to combine with another antigen to make them immunogenic and, hence, the lack of circulating antibodies to the drug itself could easily be explained.

As it does seem that all reactions to steroids are not immune mediated, what could be the other mechanisms for steroid-associated adverse events? Some of these reactions, such as cardiovascular collapse, can be explained by the rapid rate of infusion of a large dose, causing a decrease in cardiac output, secondary to an α -adrenergic blockade and direct effects on cardiac function.⁵¹ Other postulated mechanisms, although unproven, include release of histamine from mast cells, the paradoxical pro-inflammatory effect of steroids mentioned earlier,¹⁵⁻¹⁸ and transcriptional inhibition of the cyclooxygenase pathway components,¹⁴ tipping the balance toward the more bronchospastic leukotrienes.

DIAGNOSTIC MODALITIES

As for any other allergen, the gold standard test for steroid hypersensitivity should be a challenge with the putative agent (ideally double-blinded and placebo-controlled).⁵⁸ Unfortunately, few data exist in the medical literature on provocative testing, specifically for steroid-induced hypersensitivity. A few investigators have performed IV and oral challenges in their patients in a controlled setting and found them to be reliable and reproducible.^{21,24,35,59,60} However, caution must be advised because the challenge may provoke a potentially fatal anaphylactic reaction, and further, it maybe unnecessary for clinical purposes. Other less invasive tests include skin testing (either intradermal or prick testing) and in vitro tests such as the basophil histamine release test, and a variety of serologic tests for allergen specific IgE antibodies, such as the radioallergosorbent test (RAST) and the enzyme-linked immunoadsorbent assay.⁶¹ Although, in general, intradermal skin testing is more sensitive than the prick test, it is also less specific than the prick test.⁶² Very limited data are available on the utility of the in vitro tests in patients with steroid

hypersensitivity. Further, all these tests are less reliable in detecting allergies to haptenic substances, as the hapten itself may not have a cross-reacting epitope with the final macromolecular antigen that stimulated the immune response.⁵⁷ The data from case reports of patients with steroid-induced hypersensitivity clearly demonstrate this point, as several patients with reactions to steroids, even on provocative testing,²¹ have been found to have a negative skin test.^{23,24,63}

TREATMENT OPTIONS

Once a patient is suspected of having a steroid-induced hypersensitivity reaction, the suspected agent must be immediately stopped and not repeated in the future without testing. Because patients reported in the literature often have had allergic responses to more than one steroid preparation,^{21,44,48} skin testing to a variety of steroids, with and without their diluents and preservatives, must be performed to determine which component of the commercial preparation is responsible for the reaction, and also which steroid preparation, if any, is suitable for future use. Recognizing the fallibility of skin testing, any further steroid administration must be performed in a controlled setting where emergency equipment and personnel are present, and the patient be observed for 30 to 60 minutes during which time most reactions would be expected to occur. Although there is at least one report of steroid hypersensitivity being overcome in a group of patients with the use of H₁ and H₂ blockers, it is the author's personal opinion that this is too risky and therefore unwarranted.³²

Also, based on the aforementioned animal studies, when high-doses of parenteral steroids are being administered, they should be given slowly, over a 60-minute period, to minimize their hemodynamic effects.⁵¹

A more recent approach in the treatment of IgE-mediated disorders such as allergic rhinitis⁶⁴ and asthma⁶⁵ has involved the use of a humanized monoclonal anti-IgE antibody (omalizumab). By binding to free IgE, omalizumab prevents the interaction of IgE with its high-affinity receptor on mast cells and basophils, thereby preventing the release of inflammatory mediators. Although such an approach would be well suited for patients with severe IgE-mediated allergic reactions to foods and to medications including corticosteroids, there are currently no data available on the efficacy of omalizumab in this patient population.

CONCLUSION

Steroid-induced hypersensitivity is a heterogeneous entity. Although quite uncommon, it might be underrecognized because its signs and symptoms overlap with those caused by the very diseases steroids are used to treat. There are no specific demographic features that have been shown to predispose patients to develop adverse reactions to steroids, although some evidence points to a heightened susceptibility in patients with atopic conditions and those with aspirin intolerance. With advancements in medical genomics, it is perhaps not unreasonable to expect tests to become available in the near future that would help identify patients with an

immunologic profile that would put them at high risk for the development of hypersensitivity reactions. Clinical manifestations of steroid hypersensitivity range from relatively minor reactions such as urticaria to more life-threatening ones, such as bronchospasm and anaphylaxis. The mechanism of these reactions varies from a classic IgE-mediated process to direct pharmacologic effects on the cardiovascular system, with few systematic studies reported in the literature thoroughly investigating this aspect. Skin testing and RAST may offer diagnostic modalities for investigating patients with such reactions, although their sensitivity is low. Provocative challenge with the suspected agent, in a controlled environment, is the most reliable technique of confirming drug allergy. If drug allergy is suspected, the offending agent should be withheld until a suitable alternative, based on skin testing, is found. Clearly, health care professionals need to be aware that steroid hypersensitivity does exist. More detailed investigations are needed in patients with steroid-induced hypersensitivity to clarify issues related to the mechanism of the reaction.

CASE FOLLOWUP

Based on the results of skin testing, our patient was switched from IV Solu-Medrol to IV dexamethasone sodium phosphate (Decadron, Merck, West Point, PA) infusions without any problems. At last followup, 2 years later, her SLE is in remission and her Decadron infusions have been weaned off.

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CME Examination

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CME Test Questions

1. The most common adverse event related to the use of corticosteroids is:
 - a. Anaphylactic shock.
 - b. Generalized urticaria.
 - c. Behavioral changes.
 - d. Bronchospasm.
 - e. Pruritus.
2. Host factors that might predispose patients to steroid-induced hypersensitivity include:
 - a. Female gender.
 - b. Age <5 years.
 - c. History of previous drug allergy.
 - d. Concomitant use of other immunosuppressive agents.
 - e. Eczema.
3. The mechanism of steroid-induced adverse reactions is related to:
 - a. An IgE-mediated immune response.
 - b. Direct histamine release from mast cells.
 - c. Alteration in balance between leukotriene and prostaglandin synthesis.
 - d. A reaction to the diluent/preservative in the preparation.
 - e. All of the above.
4. Most systemic hypersensitivity reactions to steroids occur:
 - a. Immediately or within a few minutes of drug administration.
 - b. 4 to 6 hours after steroid administration.
 - c. 6 to 12 hours after administration.
 - d. 12 to 24 hours after administration.
 - e. At any time after drug administration.
5. The most reliable test for steroid-induced hypersensitivity reactions is:
 - a. RAST.
 - b. Passive transfer of antibody.
 - c. Intradermal skin testing.
 - d. Prick testing.
 - e. Provocative challenge.

Answers found on page 502.
