

Immediate and delayed allergic hypersensitivity to corticosteroids: practical guidelines

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Summary

Background. Corticosteroids (CS), anti-inflammatory drugs also widely used to treat various allergic diseases, may themselves give rise to immediate and delayed allergic hypersensitivity reactions.

Objectives. To realise an appropriate diagnostic work-up in order to determine the CS-allergic patient's sensitization/tolerance profile and define the potential replacement agents that can still be tolerated.

Methods. Analysis of the patch test results and concomitant (cross-) reaction patterns obtained with 315 corticosteroid-allergic patients, as well as molecular modelling of molecules.

Results. Proposal of a simplified classification of corticosteroids as to their allergenic properties into 3 groups, determination of two patient profiles according to steric and electrostatic properties of the molecules.

Conclusion. Practical information to the medical profession in order to detect and manage such reactions is provided.

Key words: allergic contact dermatitis; corticosteroids; cross-reactions; delayed hypersensitivity; guidelines; immediate hypersensitivity.

Corticosteroids (CSs) are among the most commonly used drugs, both topically and systemically. Allergic hypersensitivity reactions to CSs of the immediate and delayed types have been recognized by dermatologists since the late 1980s, although they are unexpected and paradoxical adverse effects of such drugs (1). However, such recognition is not general among other medical professionals. Knowledge of such allergies and potential cross-reactions is crucial with regard to the use of CSs in emergency therapy; hence, adequate diagnosis is essential to determine which replacement molecules can be administered, if necessary.

Delayed allergic reactions to corticosteroids (type IV reactions) (2) are common, but are not associated with immediate allergic reactions (type I) (3). They represent two different entities with regard to the frequency and clinical presentation of such reactions, the diagnostic procedures, and the cross-reaction patterns (Table 1).

Delayed Reactions

Allergic contact dermatitis is the most frequent presentation of delayed allergy; however, patients previously sensitized by topical use of a CS may also react upon systemic administration.

Frequency

The frequency of CS allergy following topical application ranges from 0.2% to 5% of all patients attending patch test clinics (4). Despite the wide use of inhaled CSs, very few cases of asthmatic patients experiencing allergic reactions have been reported (5–7).

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Table 1. Immediate and delayed allergic hypersensitivity to corticosteroids: characteristics

Reaction type	Immediate	Delayed
Frequency	Rare	Allergic contact dermatitis: frequent Systemic reactions: rare
Main sensitization/elicitation route	Intravenous	Skin (also airborne)
Influencing factors	Asthma Missing or transplanted kidney	Long-standing dermatological diseases as well as unsupervised self-treatment with low-potency corticosteroids
Clinical presentation	Urticaria, angioedema and anaphylactic symptoms Within a few minutes following corticosteroid exposure	Corticosteroid-sensitive diseases that respond poorly or not at all, or worsen following corticosteroid treatment Allergic contact dermatitis (sometimes 'edge effect') Generalized eruption Consort airborne contact dermatitis Within hours or days following corticosteroid exposure
Diagnostic procedures	<i>In vivo</i> tests: Prick 'as is' and intradermal tests (1/1000, 1/100, 1/10) with the culprit corticosteroid Biological <i>in vitro</i> tests: Tryptase levels (acute phase) Specific IgE Basophil activation test	<i>In vivo</i> tests: Patch tests with late readings (D6–D7) with the corticosteroid markers (tixocortol pivalate 0.1% pet., budesonide 0.01% pet., and hydrocortisone 17-butyrate 1% ethanol), and with the culprit corticosteroids or topical formulations used Intradermal tests with late readings, but not for routine use (risk of atrophy) Biological <i>in vitro</i> tests: research tools
Molecules most frequently involved	Methylprednisolone and hydrocortisone (particularly succinate ester substituted molecules)	Hydrocortisone and methylprednisolone and esters, budesonide (molecules without C ₁₆ -methyl substitution or halogen substitution)
Potential cross-reactivity patterns and classification	Unclear Hydrocortisone and methylprednisolone: frequent cross-reactivity	Group 1: for example, hydrocortisone, methylprednisolone, and budesonide Group 2: for example, triamcinolone acetonide, amcinonide, and desonide Group 3, for example, betamethasone, dexamethasone, diflucortolone valerate, clobetasol propionate, and mometasone furoate Two patient profiles: Profile 1: allergic to group 1 only Profile 2: potentially allergic to all corticosteroid molecules
Strategy (replacement molecules)	Systematic/individualized evaluation of the sensitization/tolerance profile Betamethasone and dexamethasone: still tolerated in many cases	Patient profile 1: molecules from Groups 2 and 3 Patient profile 2: systematic/individualized evaluation of the sensitization/tolerance profile

The prevalence of systemic allergic reactions to CSs has not been determined but is low, and it is not clear whether all patients with allergic contact dermatitis caused by CSs will react when systemically re-exposed (1, 8).

Main sensitization/elicitation route

There are many different CS molecules and several ways of administering them.

The skin is the most likely sensitization route following direct cutaneous application, but indirect contact, including airborne exposure, also occurs; indeed, contact dermatitis and primary sensitization has been induced in healthcare workers and family members by airborne exposure to budesonide-containing aerosols used by patients nearby ('by proxy', connubial, or consort dermatitis) (9).

However, other routes, such as the conjunctival mucosa, nasal mucosa, respiratory tract and gastrointestinal tract may be involved (4, 10–12),

although a primary sensitizing contact with the surrounding skin cannot be excluded either.

Sensitization induction caused by systemic administration of CSs seems to occur less frequently.

Influencing factors

Long-standing dermatological diseases and, mainly, unsupervised self-treatment with CSs constitute risk factors for the development of such allergies (4).

Clinical presentations

Recognizing CS allergy can be difficult, as its clinical presentation tends to be neither specific nor spectacular (4): the clinical signs are usually minor or show completely atypical chronology. Allergy to CSs should be suspected *a priori* in cases of CS-sensitive diseases that respond poorly or not at all to CS treatment, become worse following the use of CSs, or reoccur rapidly after CS withdrawal.

Allergic contact dermatitis caused by CSs may present as chronic eczema, with the eruption often being more pronounced at the periphery of the treated zone ('edge effect'; Fig. 1). Moreover, as there may be a long delay before diagnosis, the clinical presentation can be dominated by other 'classical' side-effects, such as cutaneous atrophy, rosacea, and perioral or perinasal dermatitis (Fig. 2). In sensitized patients, ocular use of CSs may result in facial or periocular oedema and/or eczema, conjunctivitis, burning, itching, and tear production (10), whereas inhaled CSs may provoke eczematous eruptions around the orifices (nostrils, nose, and lips), with possible extension, as well as mucosal reactions, such as stomatitis, nasal congestion, and chronic rhinitis. Moreover, bronchospasm, bronchoconstriction and systemic reactions have also been observed (11).

Finally, flare-up reactions at previously affected skin sites (8) and generalized eruptions following systemic administration of CSs have been reported (13).

Diagnostic procedures

Type IV hypersensitivity can be identified by skin tests, mainly patch tests, for which it is important to test with CS allergy markers, that is, tixocortol pivalate, budesonide, and hydrocortisone-17-butyrate, the first two being included in the European baseline series (14). However, testing with the particular CS preparations used by the patient, along with all other ingredients, including additives and preservatives, is indispensable. Except for tixocortol pivalate and budesonide, for which petrolatum works well, wherever possible the CS molecules (active



Fig. 1. 'Edge effect', that is, eruption being more pronounced at the periphery of the treated zone, which can be explained by the higher allergen concentration in the centre, where there is also a more powerful anti-inflammatory effect. On the edges, however, diffusion of the corticosteroid occurs, and the concentration is therefore lower. This phenomenon tends to disappear with time, the treated zone becoming entirely eczematous.



Fig. 2. Clinical presentation dominated by 'classical' side-effects of corticosteroids, such as rosacea and perioral or perinasal dermatitis.



Fig. 3. *In vivo* diagnosis of delayed allergic hypersensitivity to corticosteroids: corticosteroid patch testing.

principles) should be diluted in ethanol, which is the most appropriate and effective method for detection of CS delayed allergic hypersensitivity (15–17) (Fig. 3). In our centres (UZ Leuven, Cliniques Universitaires Saint-Luc), 0.1% is the test concentration used, instead of 1%, as classically described in the literature (18).

Otherwise, if the active principle cannot be obtained separately, tests with the commercial preparations should be performed. Owing to the anti-inflammatory properties of CSs, late readings between 3 and 7 days are necessary (19).

Intradermal tests with late readings should not be performed routinely, because of an important risk of atrophy, particularly with CS suspensions. Intradermal test with CS solutions, diluted 30%, 10% and 1% in saline, for which no atrophy has been observed, can be used in particular cases, that is, those with a suggestive history but (false-)negative patch test results (15).

Biological (*in vitro*) diagnosis of delayed allergic hypersensitivity to CSs is being explored, but the development of such tests remains difficult, probably because of the anti-inflammatory properties of CSs (20–23).

Molecules most frequently involved

Allergic reactions are most frequently observed with CS molecules without C_{16} -methyl substitution or halogenation, such as hydrocortisone and methylprednisolone and their esters, as well as budesonide (24).

Potential cross-reaction patterns and classifications

Sensitized patients often test positive to several CSs. Although the existence of cross-reactions has been

confirmed by positive skin test reactions to CSs that were not available on the market, concomitant or subsequent reactions can never be entirely ruled out (25).

In 1989, Coopman et al. (26) classified CSs into four reacting groups, A, B, C, and D, according to clinical and structural characteristics. In 1995, Lepoittevin et al. (27) supported this classification and the central role of constituents of the D-ring by means of conformational analysis of the observed cross-reactions.

Later, Matura et al. (28), observing the particular behaviour of certain constituents of group D CS esters, proposed a further subdivision into two subgroups, the stable D1 and labile D2 esters.

In addition to the C_{16}/C_{17} substitutions, Wilkinson et al. (29) considered that the A-ring was a second reactive centre and that halogenation of the CS structure (C_6 and/or C_9) was of critical importance in the cross-sensitivity pattern.

On the basis of patch test results and molecular modelling of CSs, we were recently able to simplify this classification of CSs into three different groups (30): group 1, the non-methylated, most often non-halogenated molecules (group A, group D2, and budesonide), which produce most of the allergic reactions; group 2, the halogenated molecules with a C_{16}/C_{17} *cis*-ketal/diol structure (acetonide group B); and group 3, the halogenated and C_{16} -methylated molecules (group C and group D1), which only rarely produce allergy (Table 2). This represents a simplification as compared with previous classifications (26–28). However, some patients may also react exclusively to budesonide (*R*-isomer, 27) along with molecules from the acetonide group. Indeed, budesonide represents an equal mixture of two isomers (*R* and *S*), the *R*-isomer resembling the acetonides, the *S*-isomer the ester group, hence possible cross-reactivity with both group 1 and 2 molecules (27, 31).

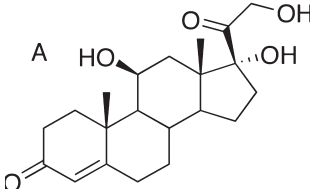
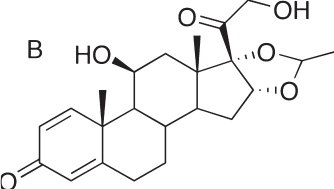
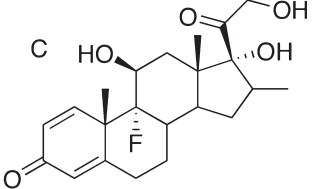
Moreover, two subgroups of patients have been identified: profile 1 patients, who react to molecules from one unique group, that is, group 1; and profile 2 patients, who may react to the entire spectrum of CSs, that is, group 1 and group 2 and/or group 3. However, testing of molecules from group 2 and group 3 is necessary to determine the specific patient profile (30).

Less is known about the classification and cross-reactivity pattern of the less common delayed reactions following systemic administration of CSs, although this might be the same as with topical use (13).

Strategy

For profile 1 patients, replacement agents can be chosen within group 2 and group 3, as they only react to group 1.

Table 2. Corticosteroid classification

GROUP	1	2	3
Characteristics	No C ₁₆ -methyl substitution No halogenation (in most cases)	C ₁₆ /C ₁₇ cis ketal diol structure Halogenation (in most cases except*)	C ₁₆ -methyl substitution Halogenation (except*)
Indicative structure	 A	 B	 C
Typical members	Budesonide Cloprednol Cortisone acetate Dichlorisone acetate Difluprednate Fludrocortisone acetate Fluorometholone Fluprednisolone acetate Hydrocortisone Hydrocortisone aceponate Hydrocortisone acetate Hydrocortisone-17-butyrate Hydrocortisone-21-butyrate Hydrocortisone hemisuccinate Isofluprednone acetate Mazipredone Medrysone Methylprednisolone aceponate Methylprednisolone acetate Methylprednisolone hemisuccinate Prednicarbate Prednisolone Prednisolone caproate Prednisolone pivalate Prednisolone sodium metasulphobenzoate Prednisolone succinate Prednisone Tixocortol pivalate Triamcinolone	Amcinonide Budesonide (R-isomer) [^] Desonide* Fluchloronide Flumoxonide Flunisolide Fluocinolone acetonide Fluocinonide Halcinonide* Triamcinolone acetonide Triamcinolone benetonide Triamcinolone diacetate Triamcinolone hexacetonide [^] may exceptionally only cross react with the acetonides	Alclomethasone dipropionate Beclomethasone dipropionate Betamethasone Betamethasone 17-valerate Betamethasone dipropionate Betamethasone sodium phosphate Clobetasol propionate Clobetasone butyrate Cortivazol* Desoxymethasone Dexamethasone Dexamethasone acetate Dexamethasone sodium phosphate Diflucortolone valerate Diflorasone diacetate Flumethasone pivalate Fluocortin butyl Fluocortolone Fluocortolone caprylate Fluocortolone pivalate Fluprednidene acetate Halomethasone Meprednisone* Fluticasone propionate Mometasone furoate

For profile 2 patients, a classification, despite being valuable for orienting the search for a replacement molecule, cannot replace systematic, individualized evaluation of their sensitization/tolerance profile. The use of a calcineurin inhibitor, that is, topical tacrolimus or pimecrolimus, may also be an option.

Immediate Reactions

It is very important to be aware of such reactions and to diagnose them, because of their life-threatening risk.

Frequency

Fortunately, immediate systemic reactions to CSs are relatively rare, with the prevalence estimated to be 0.1–0.3% (32–33).

Main sensitization/elicitation route

Immediate allergic reactions have been described following oral, intravenous, intramuscular, subcutaneous or intra-articular administration of CSs, the intravenous

route being the most frequent sensitization and elicitation route (33).

Influencing factors

Risk factors for immediate hypersensitivity reactions to CSs include asthma, and a missing or transplanted kidney. However, it is not clear whether the higher incidence of allergies in such cases is attributable to increased susceptibility or to greater exposure to CSs (13).

Clinical presentations

Symptoms such as angioedema, generalized urticaria, bronchospasm, hypotension and anaphylactic shock have been observed following systemic administration of different CS preparations (13), generally appearing within a few minutes after exposure to the culprit molecule.

Diagnostic procedure

During the acute phase of the allergic reaction, histamine and tryptase estimations can confirm an anaphylactic nature.

Within 1–3 months following this adverse event, prick and, if negative, intradermal tests with the suspected drug can be performed, with early readings. Indeed, if the prick tests are negative, intradermal tests at progressively higher concentrations (1/1000, 1/100 and then 1/10 of a saline dilution of the 'as is' corticosteroid preparation) are carried out (Fig. 4). It is also important to exclude allergic reactions to additives/preservatives, such as carboxymethylcellulose (e.g. 34) or macrogol (e.g. 35).

If the skin tests turn out to be negative, reintroduction tests can be performed with the causal CS preparation, with its vehicle components and preservative agents. However, oral provocation tests remain the gold standard for confirming or refuting the patient's hypersensitivity to a given substance.

In vitro tests such as specific IgE antibody detection and basophil activation tests may effectively complement skin tests (e.g. 36).

Molecules most frequently involved

Hydrocortisone and methylprednisolone are the systemic CS molecules that are most frequently prescribed and also implicated in immediate allergic reactions (33).

Potential cross-reaction patterns and classifications

Cross-reactivity between CSs has also been observed with immediate reactions; however, the classification and cross-reaction patterns observed with delayed reactions,



Fig. 4. *In vivo* diagnosis of immediate allergic hypersensitivity to corticosteroids: intradermal tests with early readings.

particularly allergic contact dermatitis, do not seem to be fully useful here. Indeed, in some cases, allergic reactions to hydrocortisone and methylprednisolone have been observed without cross-reactivity to other group 1 molecules such as prednisone and prednisolone (33). Several authors have also reported allergic reactions only to succinate esters of CSs, without cross-reactions with non-esterified molecules, or with those with other ester substitutions, that is, phosphate or acetate (e.g. 37). In most of these cases, however, allergic patients still tolerate halogenated molecules such as betamethasone and dexamethasone (e.g. 38, 39).

Strategy

Systematic, individualized evaluation of the sensitization/tolerance profile is necessary.

Conclusion

The allergenic potential of CS molecules should not be underestimated, delayed allergic reactions (particularly allergic contact dermatitis) being much more common than immediate reactions. The awareness and recognition

of such adverse effects and their diagnosis with adequate test procedures will allow the avoidance of recurrences of dermatitis, and, in the case of immediate reactions, possible fatal complications related to the readministration of the culprit CS molecule.

Regarding to cross-allergy patterns, there is no indication that the classification described for delayed allergic reactions is also valuable for those of the immediate type.

Finally, besides the CS molecule itself, the causative agents can also be preservatives or excipient components.

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