Original Article

# Immediate hypersensitivity to corticosteroids

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**Summary:** *Introduction:* In comparison with the extremely frequent use of corticosteroids in different diseases, immediate allergic reactions remain uncommon. In addition to the steroid molecule, the causative agent of these reactions can be an excipient.
*Material and methods:* We report seven cases of immediate reactions induced by different preparations of corticosteroids. Skin tests with the suspected steroid and excipients were carried out. In patients with negative skin tests, oral or parenteral challenges were performed with the drug and the excipients involved. Challenge tests with at least two other corticosteroids belonging to another or even the same group of the Coopman classification were carried out.
*Results:* Of the 7 patients, six had positive skin tests with the suspected preparation of corticoid: three cases with methylprednisolone acetate, two cases with carboxymethylcellulose and one case with the complete triamcinolone preparation. Only in one case did we have to challenge with the suspected steroid preparation to confirm the diagnosis.
All challenge tests with other corticosteroids belonging to another or to the same group of the Coopman classification were negative.
*Conclusions:* The reactions were caused by the steroid molecule (Triamcinolone or methylprednisolone succinate) in four patients, by an excipient (carboxymethylcellulose) in another two patients and we could not identify the sensitized molecule in one patient.
We did not demonstrate cross-reactivity between different corticosteroids.

**Key words:** carboxymethylcellulose, corticosteroids, hypersensitivity, methyl-prednisolone, triamcinolone.

**Resumen.** *Introducción:* En comparación con la elevada frecuencia de uso de los corticosteroides en distintas enfermedades, es poco común que se produzcan reacciones alérgicas inmediatas. A parte de la molécula esteroidea, el agente causal de estas reacciones puede ser un excipiente.
*Material y métodos:* Se notificaron siete casos de reacciones inmediatas inducidas por distintas preparaciones de corticosteroides. Se llevaron a cabo pruebas cutáneas con el esteroide y los excipientes sospechosos. En pacientes con pruebas cutáneas negativas se realizaron pruebas de provocación parenteral u oral con el fármaco y los excipientes correspondientes. Se efectuaron pruebas de provocación con al menos otros dos corticosteroides pertenecientes a un grupo distinto, o incluso al mismo grupo, de la clasificación de Coopman.
*Resultados:* De los 7 pacientes, 6 obtuvieron resultados positivos en las pruebas cutáneas con la preparación de corticosteroides sospechosa: 3 casos con acetato de metilprednisolona, 2 casos con carboximetilcelulosa y 1 caso con la preparación de triamcinolona completa. Sólo en un caso tuvimos que realizar una prueba de provocación con la preparación del esteroide sospechoso para confirmar el diagnóstico. Todas las pruebas de provocación con otros corticosteroides pertenecientes a otros o al mismo grupo de la clasificación de Coopman fueron negativas.
*Conclusiones:* Las reacciones fueron producidas por la molécula esteroidea (triamcinolona o succinato de metilprednisolona) en 4 pacientes y por un excipiente (carboximetilcelulosa) en otros 2 pacientes, y no se pudo identificar la molécula sensibilizante en un paciente. No se pudo demostrar reactividad cruzada entre los distintos corticosteroides.

**Palabras clave:** Carboximetilcelulosa, corticosteroides, hipersensibilidad, metilprednisolona, triamcinolona.

## Introduction

Corticosteroids are chemical compounds of hormonal nature derived from cholesterol.

Their biological power and actions depend on their chemical structure.

Due to the remarkable anti-inflammatory and immunoregulatory effects of the corticosteroids, they have been employed as first step in the management of different diseases, and sometimes they are the only possible drug to use in daily medical practice. Despite their clinical efficacy, they can induce multiple severe adverse effects [1].

In comparison with the extremely frequent application of corticosteroids in different diseases, immediate allergic reactions remain uncommon.

*Table 1*. Clinical pictures and implicated drugs.

| Patient | Corticosteroid | Clinical picture | Prick-test | ID | Challenge | Tolerated corticosteroids |
|---|---|---|---|---|---|---|
| 1 male 54-year-old | Trigon depot® Triamcinolone + carboxymethycellulose + Tween 80 + Benzylalcohol | Urticaria Angioedema | Trigon® depot: (-) | (-) | POSITIVE (urticaria | Dexamethasone Budesonide Deflazacort |
| | | | Triamcinolone | (-) | NP | |
| | | | CMC (-) | (-) | NEGATIVE | |
| | | | Tween 80 (-) | (-) | NEGATIVE | |
| | | | Benzylalcohol (-) | (-) | NEGATIVE | |
| 2 female 47-year-old | Trigon depot® Triamcinolone + carboxymethycellulose + Tween 80 + Benzylalcohol | Urticaria | Trigon® depot: (-) (-)* | (1/100) (+) (-)* | NEGATIVE* | Methylprednisolone Dexamethasone Budesonide Deflazacort Bethamethasone |
| | | | Triamcinolone (-)* | (-)* | NEGATIVE* | |
| | | | CMC (-)* | (-)* | NEGATIVE* | |
| | | | Tween 80* (-)* | (-)* | NEGATIVE* | |
| | | | Benzylalcohol (-)* | (-)* | NEGATIVE* | |
| 3 female 69-year-old | Trigon depot® Triamcinolone + carboxymethycellulose + Tween 80 + Benzylalcohol | Anaphylaxis | Triamcinolone with CMC (+) | NP | NP | Methyl-prednisolone Deflazacort |
| | | | CMC (+) | NP | NP | |
| 4 male 38-year-old | Trigon depot® Triamcinolone + carboxymethycellulose + Tween 80 + Benzylalcohol | Anaphylaxis | Triamcinolone with CMC (+) | NP | NP | Dexamethasone Budesonide |
| | | | CMC (+) | NP | NP | |
| 5 female 63-year-old | Urbason® Methyl-prednisolone succinate | Anaphylaxis | Methyl-prednisolone succinate+ | NP | NP | Betamethasone Budesonide Deflazacort Triamcinolone Hidrocortisone |
| 6 male 72-year-old | Urbason® Methyl-prednisolone succinate | Anaphylaxis | Methyl-prednisolone (+) | NP | NP | Betamethasone Triamcinolone |
| 7 female 76-year-old | Urbason® Methyl-prednisolone succinate | Urticaria | Methyl-prednisolone (-) | (+) (1/100) | NP | Betamethasone Triamcinolone Deflazacort Budesonide |

Skin and challenge test results. * Skin tests and challenge tests performed nine months after the reaction. NP: test not performed.

 

For the classification of allergic reactions attributable to corticosteroids, delayed allergic reactions after topical application have to be distinguished from immediate reactions after systemic application.

Contact allergy to corticosteroids has been increasingly recognized worldwide as a problem of considerable clinical and therapeutic importance. The incidence of corticosteroid allergy observed (from 0.5% to 5%) varies from one center to another [2].

Immediate allergic reactions such as generalized cutaneous eruption, severe respiratory distress or collapse are less frequent but may also occur. To date, there have been approximately 100 published reports of immediate hypersensitivity reactions occurring after oral and parenteral administration of corticosteroids [3]. Both immunologic and nonimmunologic mechanisms are proposed, but there is no definitive evidence in favor of either hypothesis. The pathogenesis of these immediate reactions is obviously not homogeneous. Cases with positive prick-tests or intracutaneous tests indicating IgE-mediated mechanism have been described. In cases of negative cutaneous tests, idiosyncrasy similar to reactions to acetylsalicylic acid was suspected [4]. When a patient presents delayed hypersensitivity to one corticosteroid, there is a usual cross-reaction with others belonging to the same structural group [5]. Nevertheless, there are few studies about the possibility of extrapolating such cross-reaction patterns to immediate reactions to corticosteroids.

In this article we report seven cases of immediate reactions induced by different preparations of corticosteroids.

An allergologic study with the involved drug was made to confirm the diagnosis.

We also made cutaneous and challenge tests with other corticosteroids that were not implicated in the reaction, so we could offer an alternative and safe treatment if it were necessary.

## Material and methods

*Patients:* We studied all the patients (seven patients) who consulted us about an immediate reaction after systemic corticosteroid administration in the last two years (Table 1).

Skin tests with the drugs involved (corticosteroids and local anaesthesic) and excipients were carried out on the volar side of the forearm [6]. All the above reagents were initially tested by using the prick method, and reactions were considered positive when a wheal of more than 3 mm in diameter was present 20 minutes later. When prick test responses were negative, and it was possible, 0.02-0.05 ml of the reagent solution was injected intradermally. Readings were made 20 minutes after injection. Results were considered positive when wheal and erithema greater than 5 mm were present. Positive control for prick-test was done with histamine (at 10 mg/ml). Normal saline was used as a negative control for prick and intradermal tests. Ten non-atopic and ten atopic subjects were also tested as a control.

The concentrations used in prick and intradermal tests are summarized in Table 2.

In patients with negative skin tests, oral or parenteral challenges were performed with the drug and the excipients involved until therapeutic doses were reached.

When a corticosteroid was proved as causant of the reaction, challenge tests with at least another two corticosteroids belonging to another or even the same group of the Coopman classification were carried out.

*Table 2.* Corticosteroids and local anesthetic concentrations used in skin tests.

| LOCAL ANESTHETIC | Prick test | ID | ID |
|---|---|---|---|
| Procaine 1% | 20 mg/ml | 0.2 mg/ml | 2 mg/ml |
| Lidocaine 2% | 20 mg/ml | 0.2 mg/ml | 2 mg/ml |
| Mepivacaine | 20 mg/ml | 0.2 mg/ml | 2 mg/ml |
| Articaine 40 mg/cc | 40 mg/ml | 4 mg/ml | 8 mg/ml |
| Bupivacaine 0.5% | 5 mg/ml | 0.005 mg/ml | 0.05 mg/ml |
| CORTICOIDS | Prick test | ID (1/100) | ID (1/10) |
| Betamethasone (C) | 4 mg/ml | 0.04 mg/ml | 0.4 mg/ml |
| Dexamethasone (C) | 4 mg/ml | 0.04 mg/ml | 0.4 mg/ml |
| Hydrocortisone (A) | 100 mg/ml | 1 mg/ml | 10 mg/ml |
| Methyl-prednisolone (A) | 40 mg/ml | 0.4 mg/ml | 4 mg/ml |
| Budesonide (B) | 0.25 mg/ml | 0.0025 mg/ml | 0.025 mg/mit |
| Triamcinolone (B) | 40 mg/ml | 0.4 mg/ml | 4 mg/ml |
| Prednisone (A) | 30 mg/ml | * | * |
| Prednisolone (A) | 13 mg/ml | * | * |
| Deflazacort (A) | 30 mg/ml | * | * |
| EXCIPIENTS | Prick test | ID (1/1000) | ID (1/100) |
| Carboxymethylcellulose | 5 mg/ml | 0.005 mg/ml | 0.05 mg/ml |
| Tween 80 | 0.4 mg/ml | 0.004 mg/ml | 0.04 mg/ml |
| Benzylalcohol | 10 mg/ml | 0.1 mg/ml | 1 mg/ml |

A, B, C: Groups of the Coopman classifiction.

Each patient was carefully monitored during the study, and adequate equipment for attending to any adverse reaction was on hand.

## Results

In four patients, a local anaesthetic was implicated in the reaction. Skin test with local anaesthetics were performed in these patients with negative results (Table 2). Subcutaneous challenge tests with the suspected anesthetic were also negative.

Of the 7 patients, six had positive skin tests with the suspected preparation of corticoid.

In patient no 1 who had suffered an adverse reaction to Trigon®, we had to challenge with Trigon® depot to confirm the diagnosis. This patient reacted to the challenge: he experienced generalized pruritus and urticaria 30 minutes after finishing the test. In this case we discarded the excipients as causative because subsequent skin testing and subcutaneous challenge with carboxymethylcellulose to 8 mg, Tween 80 to 0.4 mg and benzylalcohol to 10 mg were negative.

In case no 2, the intradermal test with Trigon® depot was initially positive. However, nine months later we performed the complete study with the different compounds and it was negative. The intramuscular challenge test with Triamcinolone and subcutaneous challenge with the excipients benzylalcohol and Tween 80 were negative. Moreover, at this moment the intradermal test with Trigon® turned negative and an intramuscular challenge test with the complete preparation was also negative.

In cases nos 3 and 4 we had positive skin prick test with carboxymethylcellulose, supporting the conclusion that the reactions were also produced by an excipient and not by the corticosteroids.

We confirmed the diagnosis in cases nos 5, 6 and 7 who had suffered an adverse reaction to methyl-prednisolone by means of skin test. In cases nos 5 and 7, the prick-test with methyl-prednisolone-succinate was positive. In case no 6, the intradermal test with the drug was positive at 0.4 mg/ml.

In case no 7 we also performed prick tests and intradermal tests with methylprednisolone acetate; they were negative.

All challenges carried out with differente corticoids were negative in all patients, even with drugs belonging to the same group of Coopman classification.

## Discussion

Allergic reactions due to systemic corticosteroid therapy are not frequent. Nevertheless, they should be borne in mind, since IgE-mediated and non-IgE-mediated reactions with this kind of drug or their excipients are possible.

There are several publications about Trigon® depot hypersensitivity but to our knowledge we confirmed the first case of triamcinolone allergy since in case no 1 we ruled out the role of excipients (carboxymethylcellulose, Tween 80 and benzylalcohol) by means of subcutaneous challenge. In other publications, carboxymethylcellulose was identified as the causative allergen [7-11] or the authors only investigated the role of the complete prepation, and not of the different components [12].

Patient no 2 was initially diagnosed with a hypersensivity to Trigon® depot because in the first set of cutaneous tests we only proved the role of the complete preparation. However, nine months later we performed the complete study and surprisingly all the cutaneous tests with the whole preparation and with the different parts resulted negative. Probably, the interval of nine months between the reaction and the second cutaneous test was too long, and spontaneous decrease of hypersensitivity may have taken place, as is known from other types of allergic drug reactions, such as the penicillins [13].

Two of our reactions (patients 3 and 4) are produced by the excipient sodium carboxymethylcellulose (SCMC). SCMC is the sodium salt of a polycarboxymethyl ester of cellulose. It is used in injectable preparations as a suspending agent to promote solubilization of compounds with poor water solubility. These include corticosteroids, hormones like LHRH or somatostatin. Carboxymethylcellulose is also used in cosmetics as adsorbent, anticaking agent, emulsion stabilizer, bulking agent and viscosity-increasing agent, and it is the osmotically active ingredient in some hydrocolloid wound dressings. In food, carboxymethylcellulose is labeled as E-466. Although it is widely used, few adverse reactions have been described in the literature [7-11, 14, 15]. The adverse reactions are related to parenteral administration, because SMCM is not orally absorbed**.** Only one report about anaphylaxis after orally administered carboxymethylcellulose has been published [14].

Bigliardi et al [11] suggest performing an oral provocation test against carboxymethylcellulose to exclude a reaction to small oral doses of this widely used carbohydrate. But patients allergic to carboxymethylcellulose usually do not react to the oral application of a small amount of carboxymethylcellulose typically present in food and tablets. For this reason, we recommend that these patients do not receive orally radiographic contrast media containing large amounts of carboxymethylcellulose, which increases the possibility that it may be absorbed. They also should avoid the use of hydrocolloid dressings and injectable hormone containing carboxymethylcellulose [15].

Tween 80 and Benzylalcohol are another two excipients used in pharmaceutical products. Even though they are widely used, immediate or delayed allergy to these excipients is not common but possible [16-26]. We tested these two excipients in our patients with negative results.

Patients 5, 6 and 7 were sensitized to methylprednisolone succinate. In case no 7, the prick-test and intradermal tests with another methylprednisolone ester (methylprednisolone acetate) were negative. For this reason, we assumed an adverse reaction attributable to this specific succinate ester of the corticosteroid.

 

As corticosteroids are poorly soluble in water or saline, they are coupled with esters, particularly in the position of C21 to make them water-soluble for intravenous application. Different esters such as succinate ester, phosphate ester, or others can be used [27]. Succinate ester especially seems to have immunologic potential, but the mechanism has not been finally clarified. Because of their low molecular weight, corticosteroids probably only act as haptens. Succinate ester has been suggested as possibly producing complexes of selective antigenicity [28-30].

However, different results have been published by other authors, eg, one prick test was positive only to corticosteroids without succinate ester and prick tests were negative to all derivates with succinate ester [31].

Cross-reactivity has been observed between different topical corticosteroids, but the classification of cross-reactivity between topical corticosteroids does not seem to be completely useful in adverse reactions to systemic corticosteroids.

We did not demonstrate any cross-reactivity between different corticosteroids. Four of five patients allergic to the corticoid involved had positive skin-test with this steroid molecule and negative skin-test with other steroids tested. In addition, all patients with confirmed hypersensitivity to a steroid, by means of skin-tests or challenge tests, tolerated several corticosteroids even belonging to the same group of Coopman's classification.

In other studies, different patterns of cross-reactivity have been reported:

Acero et al described a case of anaphylaxis induced by methylprednisolone (which belongs to the A group), who was also sensitized to other corticosteroids belonging to this group (hydrocortisone, prednisolone) but not to the C group corticosteroids [32]. Burgdorff et al described the case of a patient allergic to methyl-prednisolone sodium succinate with cross-reactivity between different succinate esters: methylprednisolone-21-sodium succinate and prednisolone-21-sodium succinate, while other corticosteroids without this particular ester or with other substitutions at the C21 remained negative both in the prick and the challenge tests [33]. López-Serrano et al reported two cases of cross-reactivity between paramethasone and betamethasone (corticosteroids with similar structure: having a 16 carbon methyl group, and fluoride or methyl radicals on the 6 carbon) and methyl-prednisolone that only differs from that of other corticosteroids in its 6 carbon methyl group [34].

These authors concluded that allergic reactions due to only one corticosteroid could probably be based on the allergenic properties of the original molecule. However, when there are two or more corticosteroids implicated in the reactions, the epitope is probably a product of the methabolism present in every causal drug.

In conclusion, the allergic reaction may thus be caused by the steroid molecule itself, its ester or the excipients in the preparation. Therefore, different patterns of cross reactivity have been described. Some authors report allergy to corticosteroids belonging to the A group of Coopman classification [32]. Other authors describe cross-reactivity between different succinate esters [33] or between steroids with similar chemical structure although they belong to different groups of Coopman classification [34]. Finally, we did not detect any type of cross-reactivity.

Corticosteroid allergy has very important therapeutic consequences.

Because of the occurrence of a few cases of cross-reactions between different corticosteroids, sensitive patients, in general, should be further tested with different corticosteroids with cutaneous and challenge test. Since not all patients with corticosteroid-induced reactions have been studied systematically, the sensitivity, specificity, and positive and negative predictive values of skin tests in patients with steroid-induced hypersensitivity reactions remain unknown. We propose that treatment consist of substituting the steroid with several preparations which can be tolerated by the patient on challenge test. Further studies are needed to study the value of skin-tests and the cross-reactivity of systemic corticosteroids.

In conclusion, we report seven cases of specific adverse reactions caused by different preparations of corticosteroids. Skin-tests showed an immunologic hypersensitivity mechanism in six cases and challenge tests a possible immunologic hypersensitivity mechanism in the other case. The reactions were caused by the steroid molecule in four patients and by an excipient in another two patients. We could not identify the sensitized part in the other patient. In this study we did not demonstrate cross-reactivity between different corticosteroids.

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