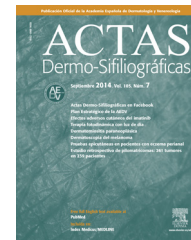




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## REVISIÓN

# Hypersensitivity Reactions to Corticosteroids<sup>☆</sup>



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### KEYWORDS

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### PALABRAS CLAVE

Dermatitis de contacto alérgica;  
Reacciones de hipersensibilidad;  
Pruebas epicutáneas;  
Batería estándar;  
Corticoides

**Abstract** Corticosteroids are widely used in clinical practice. In dermatology, their application is generally topical. These substances may act as allergens and produce immediate and delayed hypersensitivity reactions. Allergic contact dermatitis is the most frequent presentation of corticosteroid allergy and it should be studied by patch testing in specific units. The corticosteroids included in the Spanish standard battery are good markers but not ideal. Therefore, if those makers are positive, it is useful to apply a specific battery of corticosteroids and the drugs provided by patients. Immediate reactions are relatively rare but potentially severe, and it is important to confirm the sensitization profile and to guide the use of alternative corticosteroids, because they are often necessary in several diseases. In this article we review the main concepts regarding these two types of hypersensitivity reactions in corticosteroid allergy, as well as their approach in the clinical practice.

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### Reacciones de hipersensibilidad a corticoides

**Resumen** Los corticoides son fármacos ampliamente utilizados en la práctica clínica, especialmente de forma tópica en dermatología. Estas sustancias pueden actuar como alérgenos y producir tanto reacciones de hipersensibilidad inmediata como retardada. La alergia en forma de dermatitis de contacto es la reacción más frecuente, y debe estudiarse mediante pruebas epicutáneas en unidades especializadas. Actualmente la batería estándar española tiene buenos marcadores para su detección, pero no ideales. Por ello, es rentable aplicar una batería específica de corticoides si dichos marcadores son positivos, así como los corticoides propios aportados por los pacientes. En cuanto a las reacciones de hipersensibilidad inmediata, son mucho menos habituales, pero potencialmente más graves. Debido a que estos fármacos son necesarios en múltiples enfermedades, es importante confirmar la sensibilización a estas sustancias, y orientar

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el uso de corticoides alternativos. En el presente artículo pretendemos revisar los principales conceptos respecto a estos 2 tipos de reacciones de hipersensibilidad en la alergia a corticoides, así como su abordaje en la práctica clínica.

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## Introduction

Corticosteroids are widely used in dermatology, especially as topical drugs. In 1952, Sulzberger and Witten<sup>1</sup> synthesized a topically active compound called substance F, which was later known as hydrocortisone or cortisol. Since their introduction, corticosteroids have proven highly efficacious as anti-inflammatory and immunomodulatory drugs, although, paradoxically, they can behave as allergens, leading to hypersensitivity reactions. This effect was first reported in the 1950s,<sup>2-5</sup> and, since then, many more cases have been reported. Type IV (delayed) hypersensitivity reactions, which occur with symptoms of allergic contact dermatitis (ACD), are more common than type I (immediate) reactions, which are less well-known.<sup>6</sup>

Given that corticosteroids share a similar structure, cross-reactions between them are not uncommon. Consequently, it is difficult to study sensitization to these substances. Several authors have tried to classify the drugs into different groups. A current classification applied in ACD divides corticosteroids into 3 groups and patients into 2 groups, thus providing us with a more practical means of assessment. However, no ideal classification has been designed to date, and disagreement is common in daily clinical practice. Furthermore, this classification does not enable us to group the cross-reactions observed in immediate hypersensitivity reactions to corticosteroids.

Despite the fact that corticosteroids were named contact allergen of the year in 2005,<sup>7</sup> corticosteroid allergy has received little attention and constitutes a challenge in clinical practice. The presentation and diagnostic test results are often difficult to interpret and subject to peculiarities that are worthy of analysis. In suspected allergic reactions to corticosteroids, it is important to identify both the culprit drug and drugs that can be used as alternatives, since corticosteroids may become almost indispensable for the control or treatment of specific diseases.

The present article reviews key concepts in both types of hypersensitivity reaction to corticosteroids and examines their management in clinical practice.

## Types of Allergy

Corticosteroids can give rise to type I hypersensitivity reactions (immunoglobulin [IgE]-mediated), which occur only minutes after exposure, and type IV hypersensitivity reactions (T cell-mediated), which occur hours or days after exposure. In the latter, the characteristics of T cells have been studied, and analysis of skin biopsy specimens has revealed an inflammatory infiltrate composed of CD3<sup>+</sup> T cells with a predominantly type 2 helper T-cell cytokine profile.<sup>8</sup> **Table 1** shows the main characteristics of both types of reaction.

## Delayed Hypersensitivity Reactions

### Epidemiology

The frequency of ACD to corticosteroids reported in the literature ranges from 0.2% to 5%.<sup>9</sup> In Spain, the prevalence of sensitization to corticosteroids is 1.1% in patients analyzed using patch tests,<sup>10</sup> which is lower than those reported in Europe (2.6%)<sup>11</sup> and the United States (4.6%).<sup>12</sup> The main allergen in Spanish series is budesonide,<sup>13,14</sup> whereas in the United States it is tixocortol.<sup>15</sup> The sensitization rates for budesonide, tixocortol, and hydrocortisone 17-butyrate seem to be similar in Europe.<sup>16</sup>

Variations in the prevalence of ACD to corticosteroids resulting from delayed hypersensitivity reactions could be due to a series of factors, such as the frequency of corticosteroid use in each country, prescription habits, knowledge of allergy to corticosteroids, and the diagnostic tests used.<sup>17</sup> In this sense, the concentrations of corticosteroids used in patch tests in Europe are lower than in the United States.

Delayed hypersensitivity to corticosteroids is more common in women. The patients who are most predisposed to ACD to corticosteroids are those with chronic skin diseases (eg, chronic eczema, atopic dermatitis, stasis dermatitis, chronic ulcers), owing mainly to alteration of the skin barrier and the proinflammatory nature of the drugs. Corticosteroid-based self-medication without medical supervision is another predisposing factor. Genetic predisposition has also been postulated.<sup>18</sup>

## Etiology and Pathogenesis

### Routes of Sensitization/Sources of Exposure

The most common route of sensitization to corticosteroids is direct contact with the skin, although there have also been reports of indirect contact via airborne mechanisms, for example, in the case of patients with relatives who use a budesonide inhaler.<sup>19,20</sup> Other routes of sensitization include the conjunctival mucosa, nasal mucosa, respiratory tract, and gastrointestinal tract, although these are less common.<sup>21-23</sup>

### Cross-Reactions and Classification

The basic structure of corticosteroids is the cyclopentanoperhydrophenanthrene ring. Modification of this ring through halogenation and/or esterification improves the drug's therapeutic properties, thus enabling it to better penetrate the skin and increasing its effectiveness and potency. However, this chemical similarity leads to frequent cross-reactions, which are difficult to interpret. Several authors have tried to classify corticosteroids into groups in order to better understand sensitization to them.

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