

Immediate and delayed hypersensitivity to corticosteroids

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Summary

Corticosteroids are therapeutic agents used in cases of allergy and intolerance. Due to the antiinflammatory effects of the corticosteroids, hypersensitivity reactions often are considered to be a paradox. However, delayed-type reaction to corticosteroids is a frequent phenomenon in the daily routine. Non-responding eczema, development of subacute contact eczema, systemic contact dermatitis or maculopapular exanthemas can be a clinical symptom of a delayed-type hypersensitivity reaction to corticosteroids. Immediate-type hypersensitivity reactions to corticosteroids remain uncommon. Nevertheless, they can take a severe clinical course. Patients react with anaphylaxis after systemic administration or with aggravation of an allergic reaction under therapy with corticosteroids. Allergologic testing is necessary for diagnosis and providing alternative corticosteroids in case of an emergency.

Introduction

Corticosteroids (CS) are the most frequently prescribed class of medications for the topical and systemic therapy of allergies and intolerance reactions. Due to their antiphlogistic and immunosuppressive effects allergies to CGS appear unusual. In fact, the incidence of contact allergies towards CS in various epidemiological studies is reported in the range of 0.5–6 % depending on the population [1, 2]. Immediate-type reactions to systemic CS are distinctly less common; overall there have been over 100 published cases [3]. Due to the far-reaching therapeutic consequences allergological clarification and the definition of alternative preparations are mandatory.

Pharmacological mechanisms of corticosteroids

CS act primarily via a cytosolic receptor which is reached by diffusion through the cell membrane [4, 5]. By binding to the receptor this is transformed and

translocated to the cell nucleus. Here the transcription of CS-dependent genes is impacted by transactivation (induction of transcription) and transrepression (inhibition of the transcription of CS-dependent genes) [4].

The mechanism discussed for the early effect of membrane stabilization with administration of high CS doses results from the insertion of the CS molecule in the plasma membrane of immune cells with the impairment of ion flows [4, 6]. In the end, the immunosuppressive effect on T-cell activation is explained by physical interaction between CS and T-cell receptor. The CS receptor is an essential component of a T-cell receptor-bound multiprotein complex. Corticosteroid therapy leads to a dissociation of the protein complex, thus impairing T-cell signaling [4, 7].

Immediate hypersensitivity

Immediate hypersensitivity of CS manifests clinically as an anaphylactic reaction

following systemic administration of CS or worsening of an anaphylactic reaction during anti-allergic therapy with CS [3]. Case reports exist on immediate hypersensitivity reactions after oral, intravenous or intraarticular administration [3, 8, 9]. Often the CS preparation is not recognized as the trigger of the immediate-type reaction.

Intracutaneous testing with CS is of diagnostic significance [3, Table 1]. Comparison of the test reaction with the histamine control allows for a qualitative immediate reading. Immediate hypersensitivity to additives can often be diagnosed or excluded by analysis of the ingredients as well as possibly prick and intracutaneous testing. Subsequently exposition testing of alternatives with a CS preparation negative in skin testing can be performed [3]. Due to the increased risk of exposition testing in the event of immediate-type hypersensitivity confirmed in skin testing in face of the only limited possibilities of acute therapy

Table 1: Diagnostic algorithm.

	Immediate hypersensitivity	Delayed hypersensitivity
Manifestation/ history	- Anaphylactic reaction after systemic administration of CS - Worsening of an anaphylactic reaction during therapy with CS	Topical application: - Therapy-refractory course of a chronic eczema - Subacute development of a contact dermatitis - Systemic spread of contact dermatitis Systemic application: - Maculopapular exanthema
Diagnostics	- Exclusion of immediate intolerance of additives by means of analysis of composition - Perhaps additional prick testing of additives - Prick and intracutaneous testing of CS*	- Intracutaneous testing with delayed reading (up to 120h)* - Patch testing: - Marker substances: Tixocortol pivalate (cl. A), Budesonide (cl. B/D2) - DKG test series Corticosteroids - Perhaps supplementation depending on history “Edge-phenomenon“
Exposition testing of alter- native	- Selection of a preparation negative in the skin test** - Performance with emergency care available	- Selection of a preparation negative in the skin test - Consideration of Coopman classes - Performance with emergency care available

* Lack of a standard with respect to the selection of preparations. Our recommendation following [3, 20]: prednisolone (cl. A) methylprednisolone (cl. A), hydrocortisone (cl. A), triamcinolone (cl. B), betamethasone (cl. C), dexamethasone (cl. C). Perhaps individual modification dependent on history and question.

** In contrast to delayed hypersensitivity no standardized recommendations due to unclear pathogenesis. Consideration of Coopman classes possible.

(antihistamines, epinephrine) exposition testing is usually performed only when emergency care is available.

In recent years various mechanisms with which CS can induce an immune response in terms of immediate hypersensitivity have been discussed [3, 8, 10, 11]. Particularly the question of antigen determinants has been reported on differently in various studies. Due to the low molecular weight of CS there has been speculation that they themselves serve as a hapten. Esterification performed to increase solubility in water particularly with succinate esters appears to increase immunological potential [9]. On the other hand, contradictory recent studies point to the significance of the CS molecule itself as an epitope [3]. Finally, metabolites or additives such as carboxymethylcellulose may cause immediate-type allergy [10, 11].

Delayed hypersensitivity

The antiinflammatory activity of the preparation itself impacts the course and clinical findings of immediate-type hypersensitivity [2]. The most common

manifestation is the therapy-refractory course of a chronic eczema during CS treatment. The CS-specific antiinflammatory activity and the allergic contact dermatitis have opposing and reciprocally diminishing effects. Application of a topical product containing CS can lead to the de novo development of an allergic contact dermatitis, which typically takes a subacute course due to the anti-allergic and immunosuppressive mechanism of action. Even systemic spread of contact dermatitis after topical CS use has been reported. After systemic administration a maculopapular exanthema can be a manifestation of delayed hypersensitivity [2, 12, 13].

Intracutaneous as well as patch testing is of diagnostic significance (Table 1) [2, 14]. During intracutaneous testing a delayed reading up to 120 hours after injection of the test substance is required, which is explainable by the temporally delayed, subacute course of the eczema reaction due to the properties of the CS molecule itself [15]. For patch testing a standard test series of the German Contact Dermatitis Research Group

(Deutsche Kontaktallergie-Gruppe, DKG) is available which may be supplemented depending on the history. The challenges in reading and interpreting the patch test with CS again can be explained by the substance-specific mechanisms and properties. The antiinflammatory effects of the CS molecule inhibit or diminish the delayed reaction. The pharmacological vasoconstriction, termed “blanching” and the subsequent vasodilation as erythema interfere with the clinical signs of the eczema reaction [2]. Many of the mechanisms impacting the typical course of the delayed reaction manifest in what is termed the “edge-effect” in patch testing with highly potent CS [16]: The CS concentration and thus the antiinflammatory potency is highest in the center of the test chamber. Here, initially the delayed hypersensitivity manifesting as eczema is suppressed by the CS effects. Towards the periphery the concentration of the applied preparation diminishes due to centrifugal diffusion. The potency of the CS is no longer sufficient to suppress the eczema reaction, so that a ring-like dermatitis results at the

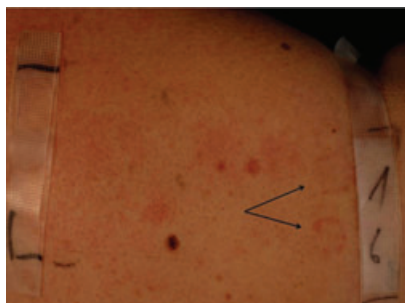


Figure 1: So-called “edge-effect” in patch testing with a strong immunosuppressive corticosteroid: peripheral eczema as a result of the concentrated anti-inflammatory effect of the corticosteroid in the center.

edge of the test chamber (Figure 1). Only in the further course the initial balance between antiinflammation and contact allergic reaction shifts in the event of strong sensitization in favor of the delayed hypersensitivity, so that clinically eczema manifests centrally also [16].

Which CS demonstrate cross-reactivity during patch test and clinically can be predicted with the help of the classification of CS by Coopman and coworkers [17]. A total of 4 corticosteroid classes were able to be defined (Table 2) [2, 17] on the basis of structural similarity of the substituents on the D ring of the steroid molecule or the carbon side chain (C₂₀, C₂₁), which increase the probability of cross-allergy and thus of a positive result in patch testing [17]. Cross-reactivity is probable within a class, but also possible between the classes through isomerization or metabolization as well as inter-individually differing metabolic pathways [2]. The mechanism of cross-reactivity allows for the definition of what are termed marker substances (tixocortol pivalate for class A, budesonide for class B and D₂) that serve a search function for contact sensitizations towards CS [2, 18, 19] (Figure 2a, b).

Additionally, the classification of CS preparations even in the event of delayed hypersensitivity allows for the selection of an alternative preparation with a low probability of cross-sensitization, which can then be exposed in the event of a negative skin test [2].

Conclusions

Immediate sensitivity towards corticosteroids is rare, but often takes a severe clinical course. Contact allergies with an incidence of up to 6 % are a relative

Table 2: Coopman classification: Classification of corticosteroids into groups of similar chemical structure. **Bold:** Eponym of the group.

Cl. A	Hydrocortisone , methylprednisolone, methylprednisolone acetate, prednisolone, prednisolone acetate, prednisone, hydrocortisone acetate, tixocortol pivalate
Cl. B	Triamcinolone acetonide , triamcinolone, budesonide, amcinonide, fluocinolone acetonide, fluocinonide
Cl. C	Betamethasone , dexamethasone, fluocortolone
Cl. D1	Clobetasol-17-propionate , betamethasone-17-valerate, betamethasone-17,21-dipropionate, mometasone furoate
Cl. D2	Hydrocortisone-17-butyrate , methylprednisolone aceponate, prednicarbate

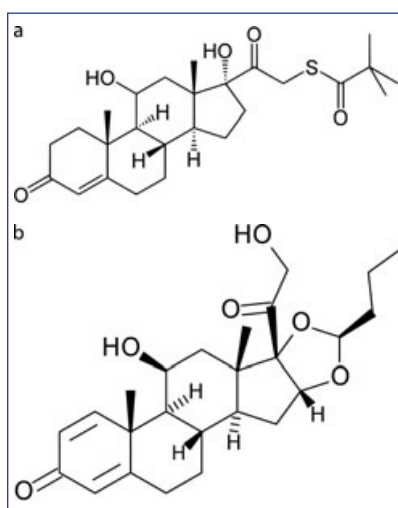


Figure 2: Marker substances acting as screening agents for contact allergy to corticosteroids. (a) Tixocortol pivalate as group A screening agent. (b) Budesonide as group B/D₂ screening agent.

common phenomenon in clinical routine, but are often not recognized initially. Allergological diagnostics serve to confirm the diagnosis and make alternative preparations available. <<<

Conflicts of interest

None.

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