

Cross-Reactivity in Cell-Mediated and IgE-Mediated Hypersensitivity to Glucocorticoids

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Abstract: In the last few decades, glucocorticoids have received increasing attention for their capability of provoking systemic hypersensitivity reactions, when administered orally, parenterally, or intralesionally, as well as allergic skin and mucosal symptoms, when applied locally to the skin in patients with contact dermatitis or to the mucosa in patients with asthma and/or rhinitis. However, because of their anti-inflammatory and immunosuppressive properties, glucocorticoids are often not suspected of such hypersensitivity reactions. In addition, because glucocorticoids retain their anti-inflammatory potential, even if they act as sensitizers, the signs and symptoms of allergic reactions are not always obvious, particularly when they overlap with those caused by the very diseases glucocorticoids are used to treat. Moreover, interpretation of diagnostic tests, specifically that of patch-test reactions, can be difficult.

In this review, particular attention is addressed to the problem of allergenic cross-reactivity among topical and systemic glucocorticoids.

We also look at the clinical and practical aspects of both cell-mediated and IgE-mediated hypersensitivity reactions to glucocorticoids and their consequences on anti-inflammatory therapeutic choices.

Key Words: Adverse drug reaction, Contact dermatitis, Cell-mediated-reaction, Cross-reactivity, Glucocorticosteroids, Hypersensitivity, IgE-mediated-reaction, Intradermal tests, Patch tests.

INTRODUCTION

Glucocorticoids (GCs) are the most efficient drugs in the treatment of autoimmune and allergic diseases; however, they are often responsible for collateral effects, especially endocrine and immunosuppressive ones [1]. Moreover, sensitization to these compounds can also occur, although not frequently. These reactions are often discovered late, especially in patients treated with several drugs [2]. In addition, the allergic sensitization to these drugs seems to be underestimated. In any case, hypersensitivity reactions to GCs are commonly reported. They can be classified as nonimmediate (or delayed) or immediate, according to the time interval between the last drug administration and their onset [3-5]. The former occur more than one hour after drug administration. After allergic contact dermatitis (ACD), the main nonimmediate reactions to GCs are maculopapular exanthems and delayed-appearing urticaria / angioedema; more rarely, fixed drug eruption, exfoliative dermatitis, generalized erythroderma, and acute generalized exanthematous pustulosis (AGEP) can be elicited [6,7]. Some evidence supports T-cell involvement in some nonimmediate reactions to

GCs, specifically maculopapular exanthems and delayed appearing urticarial eruptions [7,8]. Immediate reactions are those occurring within the first hour after drug administration and are manifested clinically by urticaria and/or angioedema, rhinitis, bronchospasm, and anaphylactic shock. They can be mediated by specific IgE-antibodies [6].

1. PATHOGENIC MECHANISMS AND RISK FACTORS FOR SENSITIZATION TO TOPICAL AND SYSTEMIC GCs

Cortisol, or hydrocortisone, represents the principal hormone of the group of steroids with 21 atoms of carbon (C), which have a C₁₇ hydroxyl group and a prevailing glucocorticoid activity, and are called 17-hydroxycorticosteroids. Cortisol is a hapten of about 400 Dalton molecular weight, whose basic structure is made up of a cyclopentanoperhydrophenanthrene nucleus, formed by the condensation of three rings of hexane with six atoms of C, called conventionally A, B and C, with a ring of pentane with five atoms of C, called obviously D. Cortisol, thanks to its size and liposolubility, which allow it to penetrate the cutaneous corneal layer, corresponds perfectly to many criteria of the ideal contact allergen [9]. Bundgaard [10] has shown that the C₂₁ position of the hydrocortisone molecule in aqueous solution is degraded to a steroid glyoxal. Glyoxals can bind covalently the guanidino groups of arginine. The stability of the

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link of the steroid hapten with cutaneous or serum proteins would therefore make it immunogenic. The transformation of the steroid hapten into a complete antigen would thus allow the presentation of the steroid rings to the immunocompetent cells.

1.1. Nonimmediate Reactions

The affinity of hydrocortisone with arginine and topical preparations that contain it in equimolar conditions could be a key factor in promoting a cell-mediated sensitization to topical GCs [11].

A pH alkaline could also promote cortisol oxidation and degradation [11], determining a higher accumulation of steroid glyoxal, which would bind to the arginine.

Generally, cutaneous pH is around a 5.5 value, but in the axillary and perineal areas these values are higher (pH equal to 7.2-8) because of heavy sweating [11].

Other conditions that promote the increase of cutaneous pH are bacterial infections of cutaneous wounds, occlusions, eczematous lesions from venous stasis, ACD and irritant contact dermatitis [11]. This could explain the association observed between ACD to topical GCs and stasis dermatitis, leg ulcers and dermatitis in the perineal area [12,13], even though, in general, all chronic dermatitis, such as hand dishydrosis, genital lichen simplex, seborrheic facial dermatitis, and atopic and contact eczema certainly are risk factors for an allergic contact sensitization to GCs [14]. In fact, it is thought that sensitization occurs in these cases because of an impaired barrier function of the skin [6,15]. Another risk factor for the development of ACD to GCs is the presence of two or more patch tests positive to other topical drugs, such as neomycin, local anesthetics or disinfectants [16].

Furthermore, the steroid glyoxal is a product of the degradation of cortisol, which contains an alpha-ketoaldehyde on C₂₁. Aldheydes are extremely toxic and unstable metabolites, probably sufficient to trigger risk signals in the organism and consequently activate the immune system [17]. Aldheydes and GCs are degraded in the organism by an aldolase (aldheyde-dehydrogenase), the same one that metabolizes alcohol and the aldheyde deriving from it [18]. In this light, it is not exceptional that the frequency of positive patch tests to ethanol is higher in patients with contact allergies to GCs [19,20].

A deficit of the aldolase activity, due to hepatic stress, chronic hepatitis, or genetic factors, could determine an accumulation of aldheydes or steroid glyoxal, increasing the risk of an allergic sensitization following the administration of systemic GCs.

1.2. Immediate Reactions

The formation of a steroidal glyoxal is also possible in the serum [10]; therefore, allergic sensitization can also appear following repeated systemic administrations of GCs.

Although cortisol is present in the blood in minimum part in a free form, it requires a protein binding, especially to the transcortin, for its transport. The binding ability of transcortin and its stability are regulated by the arginine pK. This last is influenced by the pH; when the pH is neutral or alkaline,

the guanidino groups of the arginine are not obviously exposed on the binding site [21,22].

The administration of chemically modified GCs in doses higher than those that generate physiological levels, could in fact cause the formation of serum cortisol-transcortin or cortisol-albumin conjugate compounds, which are stable and, therefore, immunogenic.

The following have been identified as risk factors for immediate reactions to systemic GCs: bronchial asthma, hypersensitivity to acetylsalicylic acid or to other nonsteroidal anti-inflammatory drugs, intravenous administration of high GC doses (bolus therapy), and a clinical history of nephritis or kidney transplantation [23].

We have identified other risk factors: autoimmune diseases, such as systemic erythematous lupus, rheumatoid arthritis, multiple sclerosis, psoriasis, lichen planus, which require frequent administration of GCs by systemic, intralesional or topical routes [24], and ACD to topical GCs, which is often unrecognized [25]. As confirmed by dermatological studies [26], percutaneous absorption can lead to hidden or underestimated sensitization.

2. CLINICAL ASPECTS

2.1. Nonimmediate Reactions

ACD is the most frequent delayed reaction to GCs; however, only in the last couple of decades, after the introduction of tixocortol pivalate in patch testing reagents as a steroid hypersensitivity marker, has the magnitude of this phenomenon been well recognized [6]. The North American Contact Dermatitis Group, a research organization of American and Canadian dermatologists who specialize in patch testing, incorporated tixocortol pivalate into the standard series in the early 1990s. From 1998 to 2000, almost 6,000 patients were evaluated: 2.7% displayed patch-test positivity to tixocortol pivalate and 1.4% to budesonide. Most of these positivities were believed to have some possible relevance [27]. In the U.K., the prevalence of tixocortol pivalate hypersensitivity was 2 to 5% in over 3,000 subjects who had undergone routine patch testing [28,29].

The most frequent clinical picture of ACD to topical GCs is a sub-acute or chronic eczematous dermatitis, which does not respond to local dermatologic treatment and even worsens following the application of topical steroid preparations [25].

GCs can also provoke nonimmediate reactions when applied locally to the mucosa in patients with rhinitis and/or asthma. Local adverse effects attributable to inhaled budesonide or tixocortol pivalate include pruritus, nasal burning, worsening of rhinitis or asthma, erythema and edema of the mouth, and a dry cough. Furthermore, systemic signs and symptoms, such as eczematous and erythematous lesions of the face and body, and urticaria, provoked by inhaled tixocortol pivalate and budesonide have been reported [30].

GCs can also sensitize individuals, and then elicit non-immediate reactions, when administered orally, parenterally, or intralesionally. The prevalence of nonimmediate hypersensitivity reactions to systemic GCs has essentially been unexamined [6]. A review by Whitmore *et al.* [31] regarding

such reactions showed that clinical manifestations were variable, but generally consisted of eczematous or exanthematous skin eruptions. In fact, together with delayed-appearing urticarial eruptions, maculopapular exanthems were the main nonimmediate reactions reported by the 38 patients recently studied by Padial *et al.* [7]. Most of these subjects had been treated for osteoarticular diseases, and GCs had been administered intralesionally in 71% of cases. More rarely, cases of exfoliative dermatitis, generalized erythroderma, erythrodermic dermatitis [32], fixed drug eruption [33], polymorphous erythema [34], AGEF [35], Stevens-Johnson syndrome [36] and toxic epidermal necrolysis (TEN) [37] associated with systemic GCs have been described [6]. Most of them are reports of single cases.

2.2. Immediate Reactions

Little is known about the exact prevalence of immediate hypersensitivity reactions to GCs [38]. However, a prospective study [39], involving 213 children with various rheumatologic diseases treated with intravenous steroids, seems to support the notion that such reactions are uncommon. In fact, immediate reactions were observed in only 0.1% of approximately 10,000 doses of GCs. Such reactions were pruritus in 9 cases, hives in 5, and anaphylactic shock in one.

The clinical signs and symptoms of immediate reactions to systemic GCs range from urticaria to sudden cardiovascular collapse and death [38]. Some of the more common reported reactions include localized or generalized urticaria, sometimes with purpuric aspects, angioedema of the face and/or periorbital edema, bronchospasm, and hypotension [24,39,38].

3. DIAGNOSTIC TESTS

3.1. Nonimmediate Reactions

Patch tests are the classic tests for evaluating patients with ACD to GCs. In fact, both the European Academy of Allergology and Clinical Immunology (EAACI) [40] and the International Contact Dermatitis Research Group (ICDRG) [41] advise their use to assess such cutaneous adverse reactions. Patch tests, together with delayed-reading intradermal tests, are also useful tools for evaluating other nonimmediate reactions to GCs, such as eczematous or maculopapular eruptions.

Because of their anti-inflammatory activity, GCs can cause problems in patch testing. In fact, if the concentration of the GC tested is too high, the anti-inflammatory effect may predominate, and patch-test results may be negative. On the other hand, if a low concentration of the GC is used for patch testing on intact skin, a negative reaction is not uncommon; such a concentration may elicit a positive reaction only when applied on eczematous skin [42].

If a high concentration of the GC is used for patch testing, the "edge effect" phenomenon may occur at the patch-test reading. This appears as induration, erythema, and papulovesicles at the outer edge of the patch-test site, but not in the center, where classic reactions to other reagents are usually observed [43]. It is thought that this phenomenon occurs because the anti-inflammatory effects of high GC concentrations predominate in the center, suppressing the

cell-mediated reaction, while the lower peripheral concentrations allow the reaction to take place [6].

Anti-inflammatory and vasoconstrictor effects of GCs may hide positive reactions after the removal of patch tests, suggesting the need for further readings 2 to 7 days later [44].

In most studies GCs were tested at a concentration of 1%. However, some authors [45,46] suggest that lower concentrations should also be used, because of the inhibition of hypersensitivity reactions at 1%. The choice of vehicles for patch testing is also important [47]. Matura and Goossens [46] used the 1% concentration of tixocortol pivalate both in ethanol and petrolatum and did not observe any statistical difference in the number of positive reactions. However, patients tested with 0.1% budesonide both in ethanol and petrolatum displayed significantly more positive reactions to budesonide in ethanol [46].

Patch tests and delayed-reading intradermal tests can display a different sensitivity, depending on the GC assessed. Generally, delayed-reading intradermal testing appears to be more sensitive than patch testing [48]. In some studies, patients with cell-mediated hypersensitivity reactions to some GCs, such as betamethasone valerate, budesonide, clobetasol propionate, hydrocortisone-17-butyrate, and triamcinolone acetonide, displayed patch-test negativity and delayed-reading intradermal-test positivity [49-51]. However, intradermal tests are not as standardized as patch tests and are difficult to perform in the case of compounds not available in an injectable form. Moreover, generalized skin reactions may be observed after intradermal testing [32].

A cellular response involving drug-related T-cell activity may be assessed *in vitro* by the lymphocyte transformation test. In a study by Wilkinson *et al.* [52], which evaluated patients with ACD to hydrocortisone by such test, stimulation indexes were statistically higher in the sensitive patients than in the control subjects.

For evaluating patients with hypersensitivity reactions to GCs, we have few diagnostic tools and their sensitivity is limited. Therefore, provocation tests are often necessary to diagnose hypersensitivity to GCs. In the recent study by Padial *et al.* [7], only 2 of the 38 patients with nonimmediate reactions to GCs displayed positive delayed-reading intradermal tests and patch tests to the responsible drug, while 21 of the 32 patients who agreed to undergo challenges reacted to them. It is important to note that provocation tests should be performed only when other allergologic tests are negative and not in patients with severe reactions. In case of positive allergologic tests, provocation tests with other GCs may allow an alternative to be found. The general considerations, including indications, contraindications, and precautions, for carrying out a drug provocation test are detailed in the recent position paper of the European Network for Drug Allergy [53]. Generally, one should start with a low dose, carefully increase this and stop as soon as the first objective symptoms occur, which also include the flare-up of previous patch tests [54,55]. If no symptoms appear, the maximum single dose of the specific drug must be achieved, and the administration of the defined daily dose is desirable. In case of previous nonimmediate reactions, the starting dose should not exceed 1:100 of the therapeutic dose. Depending

on the drug and the patient's response threshold, provocation tests may be completed within hours, days or, occasionally, weeks.

Provocation testing is particularly useful in patients displaying doubtful results in allergologic tests and in those presenting positive results to several GC molecules [56].

3.2. Immediate Reactions

Patients with immediate reactions to GCs should be evaluated first by the more specific, but less sensitive prick testing, followed, in case of negative results, by intradermal testing. Such testing is not standardized, and may provoke systemic reactions, as well as false positive results, when high concentrations are used [57,58]. Performing skin tests with serial dilutions of GCs in subjects with negative histories of adverse reactions, such as successfully done with several antibiotics [59], allows those concentrations of GCs that do not elicit irritant responses and are useful for diagnosing IgE-mediated hypersensitivity reactions to be determined. When performed, skin tests were positive in a large percentage of patients who had suffered immediate hypersensitivity reactions to GCs [23,60]. However, it is crucial to perform skin tests appropriately. There are reports of single patients who had suffered anaphylactic reactions and displayed positive skin tests to the responsible succinate esters of hydrocortisone and methylprednisolone, but who were skin-test negative to their acetate esters [61-63]. This phenomenon is caused by the different affinity for proteins, which is high for succinate salts and very low for acetate ones [64]. In any case, skin-test negativity does not exclude an immunologic pathogenic mechanism.

Recently, improvement in laboratory techniques has allowed detection of serum specific IgE to hydrocortisone and methylprednisolone in patients with immediate hypersensitivity reactions to these GCs [65-67]. Compared with the first findings at the beginning of the 1980s [68], this suggests that IgE-mediated reactions to GCs are much more widespread than it was believed.

Provocation tests are also essential for diagnosing an immediate hypersensitivity in patients displaying negative or doubtful results in skin testing. In case of a previous im-

mediate reaction, the starting dose should be between 1:10.000 and 1:10 of the therapeutic one, depending on the severity of the reaction; the time interval between doses should be at least 30 min, but specific situations might require longer intervals. A one-hour interval between each dose should be a sufficient time, considering that in the only case reported in the literature of anaphylaxis induced by oral prednisone, the symptoms appeared 40 minutes after its assumption [69].

4. THE ETIOLOGIC ROLE OF PRESERVATIVES

Preservatives contained in topical or systemic preparation of GCs can be responsible for adverse reactions.

Table 1 shows the main preservatives contained in GCs for systemic use that have been shown to be responsible for immediate hypersensitivity reactions.

Carboxymethylcellulose, or E-466, is a semisynthetic preservative of high molecular weight, used as an emulsion in many compounds, including mixtures of barium sulfate for radiological examinations [70,71] and local anesthetic gels [72]. It is the excipient most cited in the literature [73, 74] as responsible for immediate hypersensitivity reactions, in some of which serum specific IgE to it were detected [70,71,74].

Parabens [75], benzyl alcohol [76] and polyvinylpyrrolidone, or povidone-iodine [77,78] are other preservatives responsible for immediate hypersensitivity reactions, which might be erroneously attributed to GCs. In particular, specific IgE to povidone-iodine, a synthetic polymer of high molecular weight [77], have been detected in a case of generalized urticaria-angioedema after its topical application [78].

Contact sensitization to acetylstearyl alcohol, a common component in topical formulations of GCs, is 20 times more frequent in patients with ACD to GCs than in other patients with positive patch tests to other substances [79].

5. CROSS-REACTIVITY AMONG TOPICAL AND SYSTEMIC GCs

5.1. Nonimmediate Reactions

It has been observed that most patients with ACD to GCs react to several compounds. An irrefutable proof of the ex-

Table 1. Preservatives in GC Topical Preparations Responsible for Allergic Contact Sensitization

Ethyl alcohol 5% water and pure	Sorbitan-sequiolate 20% pet.
Benzyl alcohol 5% pet.*	1,2,6- hexanetriol 5% pet.
Isopropyl palmitate 5% pet.	Lanoline 30% pet.
Paraben 3% pet.	Cetostearyl alcohol 30% pet.
Chlorocresol 1% pet.	Ethylendiamine chloridrate 1% pet.
Propylen glycol 10% water	Propylgallate 0.1% pet.
Sodium bisulphite 5% pet.	Sodium lauryl sulphate 0.1% water
Diocetyl sodium sulfosuccinate 1% water	Mistril y picolinium chlorure 0.1% pet.
Polysorbate 60 5% pet.	

*pet. = petrolatum.

istence of a true allergic cross-reactivity among topical GCs is provided by reactions to patch tests with compounds to which sensitive patients have never been exposed [80]. This cross-reactivity has practical consequences for the identification of those GCs most frequently responsible for sensitization, as well as for the choice of those agents that must be used in diagnostic tests [81].

Clinical studies have led to the classification of GCs into the following four groups according to the function of their allergenicity [82]: group A, hydrocortisone type; B, triamci-

nolone acetonide type; C, betamethasone type; and D, hydrocortisone-17-butyrate type (Table 2, Fig. 1). The presence or absence of a C₁₆ methyl substitution and/or halogenation on C₉ of the B ring has led to a further structural subdivision of group D steroids into D1 and D2 groups [83]. In general, many positive reactions are observed to group A, group B, and those compounds belonging to group D2 that lack both a C₁₆ methyl and halogen substitute (e.g., hydrocortisone-17-butyrate, -aceponate, -buteprate, methylprednisolone aceponate, and prednicarbate). Steroids of group D2 show significant cross-reactivity within their own group as well as to

Table 2. Classes of Allergenic Cross-Reactivity Among Topical Corticosteroids According to Coopman and Doms-Goossens [82], as Modified by Matura and Goossens [46]

Class A (HC* type without change of the D ring or of C ₂₀ -C ₂₁ or presence of esters with brief chain on C ₂₀ -C ₂₁): HC, Prednisolone and Methylprednisolone and their ester acetates, sodium-phosphates and succinate, Cortisone, Prednisone, Tixocortol pivalate;
Class B (Triamcinolone acetonide type with C ₁₆ , C ₁₇ -cis-ketal or -diol changes): Triamcinolone acetonide, Fluocinolone acetonide, Halcinonide, Desonide, Fluocinonide, Halcinonide, Budesonide, Amcinonide, Flunisolide, etc
Class C (Betamethasone type with methylation -CH ₃ on C ₁₆ , but without esterifications on C ₁₇ -C ₂₁): Betamethasone, Dexamethasone, Paramethasone, Desoxymethasone, Fluocortolone.
Class D (Clobetasone type or HC esterification with a long chain at C ₁₇ and/or C ₂₁ and with or without methylic group at C ₁₆):
Class D1 Clobetasone-17-butyrate, Clobetasol-17-propionate, Beclomethasone dipropionate, Betamethasone valerate, Betamethasone dipropionate
Class D2 HC-17-propionate, HC-17-butyrate, Methylprednisolone aceponate, Prednicarbate

*HC = Hydrocortisone

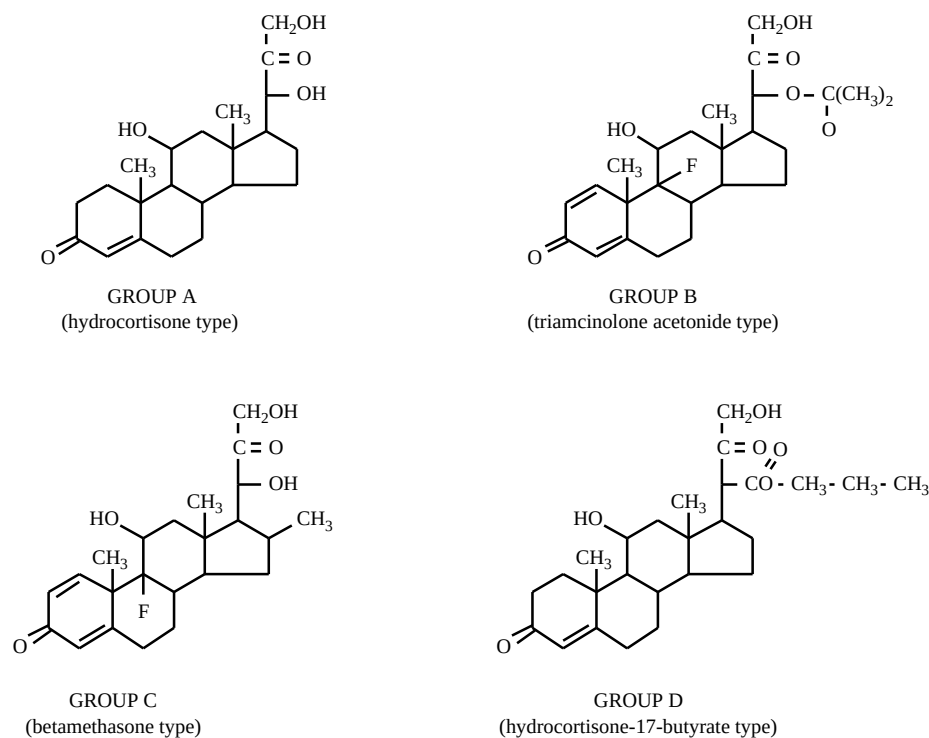


Fig. (1). The patterns of corticosteroid cross-reactivity according to Coopman and Doms-Goossens [82].

group A compounds and budesonide (group B). On the other hand, group C and those of group D1 that are C₁₆ methyl and halogen substituted (e.g., betamethasone and its esters, clobetasone and its esters, mometasone furoate, and fluticasone propionate) produce very few allergic contact reactions [46]. Compounds of group D1 exhibit minimal cross-reactivity with other steroid groups.

The existence of these groups, as defined by the analysis of cross-reaction patterns in patients with cell-mediated hypersensitivity to corticosteroids, is fully supported by the configuration analysis of these molecules. Compounds of the same group have similar spatial structures, explaining the cross-reactions observed. In addition, molecules from one group are sufficiently different from those of another one to explain the lack of cross-reactivity observed among groups A, B, and D [84].

Tixocortol pivalate and budesonide have proved to be very useful screening markers of corticosteroid hypersensitivity. Boffa *et al.* [85] patch tested 2,123 patients with a series of 6 GCs, in parallel with a standard series: a combination of tixocortol pivalate and budesonide detected 91.3% of the 127 GC-sensitive patients. Tixocortol pivalate and hydrocortisone contact allergy are definitely associated; therefore, the former is used to test for allergies to the group A compounds. Budesonide detects a different pattern of corticosteroid hypersensitivity. It is involved in cross-reactions not only with acetonides (group B, to which it theoretically belongs), but also with some of the esters of group D. This special reactivity can be explained by the structure of the acetal function, which allows the molecule to mimic either the group B or the group D molecular shape. Therefore, tixocortol pivalate (group A) and budesonide (groups B and D) should certainly be added to the standard series to screen for corticosteroid hypersensitivity [84].

However, some authors have questioned whether this classification into four groups adequately explains cross-reactivity patterns observed in clinical practice [64,86,54]. Specifically, Wilkinson [87], even though he has recently agreed on the importance of substitutions at the C₁₆/C₁₇ positions of the D ring in influencing cross-reactivity, has proposed that other rings (A-C) are also important in determining cross-reactions among GCs (Fig. 2). In fact, after having patch tested 96 patients with hydrocortisone ACD, he found that the presence of a substitution at the C₆ or C₉ position of the B ring was another important factor to consider in determining allergic cross-reactivity [86]. The presence of a halogen element atom – like chloride or fluoride on C₉ – by determining an electron-attractor effect on C₁₁ [1], may cause a refolding of the GC molecule and give it a remarkable conformation stability. Wilkinson *et al.* [88] also patch tested 46 patients with cell-mediated hypersensitivity to budesonide using 17 other topical GCs, and they observed that the modifications made on C₂₁ were useful in favoring the link with cutaneous proteins, but were not influential from an immunologic point of view, since keratinocytes have an esterase which determines a rapid hydrolysis of C₂₁ side chains and may therefore modify the class to which a topical GC belongs. The same author [87] has also emphasized that new molecules may be generated after degradation and metabolism of a topically applied GC, with the possibility of a

cross-reaction to a degradation product, but not to the parent drug, i.e., hydrocortisone-17-butyrate may cross-react with hydrocortisone after loss of the C₁₇ ester.

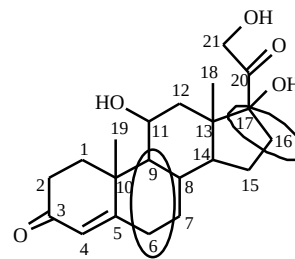


Fig. (2). Site modifications influencing corticosteroid cross-reactivity according to Wilkinson [87].

Less is known about the classification and cross-reactivity patterns of systemic steroid preparations than those of topical preparations. It is generally accepted, however, that the same cross-reactivity patterns observed for topical preparations occur when they are used systemically. Such patterns should be taken into account for choosing an alternative GC molecule in sensitive patients [89-91]. As with their topical counterparts, there will be exceptions to systemic steroid cross-reactivity patterns. Thus, there are no adequate substitutes for direct patch-testing the corticosteroid compound in question [6].

5.2. Immediate Reactions

A study, carried out with techniques of x-ray crystallography and ultramicroscopic scansion, examined the interaction between a bovine cortisol-albumin conjugate (BSA), the cortisol-3-(O-carboxymethyl)oxime-BSA, and its specific monoclonal antibody (mAb) of murine derivation, called 5A4. Such study also provided a three-dimensional computerized graphic reconstruction, in order to assess the conditions of specific antigen-antibody interaction [92]. From this ultrastructural analysis, it was found that the paratope of the specific antibody formed a pocket containing some complementary determining sites of linkage constituted by various aromatic amino acids that provided a hydrophobic environment around the steroid molecule. The mAb 5A4 showed a high affinity for cortisol-3-(O-carboxymethyl)oxime-BSA, its immunogen, but not for cortisol-21-hemisuccinate-BSA, by suggesting that the direction of the steroid molecule inside the pocket of the paratope is important for its recognition [92].

Therefore, if an antibody specific to cortisol interacts with the whole steroid molecule, we agree with Wilkinson that substitutions at C₆/C₉ and/or C₁₆/C₁₇ may influence the allergenicity of GC molecules also in the case of IgE-mediated reactions [87]. This appears to be a more suitable approach for identifying alternative molecules in cases of immediate hypersensitivity reactions to systemic GCs.

In fact, the tolerability of alternative halogenated GCs, such as betamethasone and dexamethasone, in patients who suffered immediate hypersensitivity reactions to succinate esters of hydrocortisone or methylprednisolone, besides be-

ing reported in various cases and numerous reviews [23,24], has been confirmed in two studies [60,67] that evaluated, respectively, 7 and 10 patients with IgE-mediated asthma.

However, tolerability of halogenated GCs could also be explained by their low dosage: in fact, while it has been shown that patients with an ACD to GCs can tolerate moderate or even high doses of the same steroid molecule administered systemically [54], immediate reactions are often considered nonallergic drug hypersensitivity reactions, because they may be dose-dependent [93], as reported by some authors [94, 95].

Actually, since GCs are monovalent haptens, they interact in a ratio of 1:1 with the specific paratope, as confirmed by the aforesaid ultramicroscopic study [92]. In order to provoke mast-cell activation, however, it is necessary for the hapten to establish a bridge between two specific and contiguous IgE molecules attached to the mast cell [96]. This happens when sufficiently high doses of GCs saturate the proteins of serum transport; therefore, due to the different anti-inflammatory power, the administration of 4 mg of disodiumphosphate betamethasone is quite different from the administration of 200-300 mg of succinate hydrocortisone, which is a dose of haptens 50 times higher.

In order to confirm that the tolerability of an alternative GC in the case of immediate reactions is caused by the alterations of the sites suggested by Wilkinson [87] and not by its dosage, we also used oral challenges with increasing doses of deflazacort in our study of 10 patients. The administration of a cumulative dose of 60 mg did not elicit any symptoms in the patients observed [60].

The classification of Coopman *et al.* [82] appears to be valid also in the case of immediate reactions. In fact, patients allergic to the GCs of group A (hydrocortisone and methylprednisolone) tolerate the GCs of group C (betamethasone, dexamethasone, paramethasone). Patients with immediate-type reactions to intravenous succinate esters of hydrocortisone and methylprednisolone tolerate prednisolone (a GC of group A) orally, as reported by many authors [23,24,65,66]. This is probably due to the fact that the introduction of a double binding on C₁-C₂ of the cortisol A ring increases the binding affinity of prednisone/prednisolone more than the cortisol itself for its serum binding proteins, by changing the directions of the steroid molecule, so the ring D and C₂₁ are oriented towards the pocket of the paratope [65,97] instead of the A ring as in succinate esters. From this report, oral administration proves to be preferable to intravenous, but this is true only for prednisolone [66] and methylprednisolone, because oral hydrocortisone is not tolerated by patients with IgE-mediated reactions to homonymous succinate salt [66], probably because the binding of cortisol with serum proteins takes place thanks to hydrogen binding with the hydroxyl group on C₁₇ [22].

Although the alteration carried out on C₂₁ in the case of succinate esters of hydrocortisone, prednisolone and methylprednisolone may determine a similar presentation to specific IgE, with consequent allergenic cross-reactivity among these GC molecules [23,24,65-67,97], in some cases, the presence of a methyl group on C₆, as in methylprednisolone, is sufficient to modify the allergenic properties by avoiding

cross-reactivity with hydrocortisone [68,98,99] or with prednisolone [34].

CONCLUSION

GCs can provoke either cell-mediated or IgE-mediated hypersensitivity reactions, when applied locally to the skin in patients with contact dermatitis or to the mucosa in patients with asthma and/or rhinitis, as well as when administered orally, parenterally, or intralesionally. However, because of their anti-inflammatory and immunosuppressive properties, GCs are often not suspected of such hypersensitivity reactions.

In case of hypersensitivity reactions to GCs, it is advisable to carry out allergologic tests, distinguishing between immediate and nonimmediate reactions, in order to identify the culprit drug and provide a safe alternative for sensitive patients.

ABBREVIATIONS

ACD	= Allergic contact dermatitis
AGEP	= Acute generalized exanthematous pustulosis
BSA	= Bovine cortisol-albumin conjugate
EAACI	= European Academy of Allergology and Clinical Immunology
GC	= Glucocorticoid
ICDRG	= International Contact Dermatitis Research Group
mAb	= Monoclonal antibody
TEN	= Toxic epidermal necrolysis

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