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Contact allergy to corticosteroids**

Alergia kontaktowa na preparaty glikokortykosteroidowe

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S u m m a r y

Glucocorticosteroids are among the most important and popular therapeutic agents in contemporary medicine. Contact allergy to corticosteroids is considered to be a significant diagnostic and therapeutic problem, because pharmacological (anti-inflammatory, immunosuppressive) properties of these agents often mask their ability to induce contact sensitivity reaction. The contact sensitivity reaction to haptens is a classical example of cell-mediated immune response, resulting from type IV hypersensitivity according to Gell and Coombs classification. Patch tests are considered to be the golden standard in the diagnosis of contact allergy. Sensitivity to corticosteroids is characterized with an increasing incidence. In dermatology steroids are applied in many different dermatoses, mainly in those with chronic and recurrent inflammatory origin, like atopic dermatitis or eczema. Diagnosis of contact allergy to corticosteroids increases chances for achieving complete remission and improves patients „quality of life". The review focuses on the current knowledge about contact allergy to corticosteroids which has been classified as allergens of the year 2005.

Key words: contact allergy, corticosteroids

S t r e s z c z e n i e

Glikokortykosteroidy zaliczają się do najpopularniejszych środków leczniczych stosowanych we współczesnej medycynie. Alergia kontaktowa na glikokortykosteroidy stanowi duże wyzwanie diagnostyczne i terapeutyczne, bowiem właściwości farmakologiczne (przeciwzapalne, immunosupresyjne) tych substancji często maskują ich zdolność do wywoływania reakcji nadwrażliwości kontaktowej. Reakcja nadwrażliwości kontaktowej na hapteny jest klasycznym przykładem immunologicznej reakcji komórkowej występującej wskutek nadwrażliwości typu IV wg klasyfikacji Gella i Coombsa. Za efektywną metodę diagnozy alergii kontaktowej uznawane są naskórkowe testy płatkowe. Nadwrażliwość na glikokortykosteroidy występuje coraz częściej. Steroidy znajdują zastosowanie w dermatologii w wielu różnych dermatozach, głównie przewlekłych i powiązanych z nawracającymi stanami zapalnymi, takimi jak atopowe zapalenie skóry czy egzema. Zdiagnozowanie alergii kontaktowej na glikokortykosteroidy zwiększa szansę na zupełną remisję i poprawia jakość życia pacjenta. Niniejsza praca skupia się na aktualnym stanie wiedzy o alergii kontaktowej na glikokortykosteroidy, które uznano za alergeny roku 2005.

Słowa kluczowe: alergia kontaktowa, glikokortykosteroidy

Allergic contact eczema named also allergic contact dermatitis (Latin: contact dermatitis, contact eczema) develops after a direct contact with an allergen. Clinically, two types of disease can be distinguished: an acute type (Latin: contact dermatitis acuta, eczema acutum) and a chronic type (contact dermatitis chronic, eczema chronicum) (1).

Most of the allergens evoking the disease are characterized by a low molecular weight (lower than 1000 daltons). Contact allergens are haptens, which acquire a full antigenic capacity only after binding themselves with protein in the skin. From the clinical point of view, an important factor of developing a contact allergy is a fully preserved correct function of the epidermal barrier. Mechanical damages of the epidermis, maceration, dryness, inflammation are the causes of increased hapten penetration into the skin. Occlusive bandages are factors facilitating the penetration.

Allergic contact dermatitis is a result from type IV hypersensitivity according to Gell and Coombs classification. Its development consists of two phases: induction and release. During the induction phase haptens bind in the extravascular space with serum proteins creating an immunological complex, which is then presented by

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the Langerhans cells to Th1 lymphocytes in the surrounding lymph glands. This presentation occurs with the participation of the MHC histocompatibility antigens of the II class. This leads to the formation of the specific memory Th1 lymphocytes for the presented haptens. During the next contact with a given allergen, after at least 24-48 hours, the release phase starts, which activates the specific memory Th1 lymphocytes producing the proinflammatory cytokines, such as IL-2, IFN-γ and TNF-α (2). The released cytokines are responsible for the activation and migration of the allergic reaction cells including cytotoxic lymphocytes, macrophages and neutrophiles. Keratinocytes also take part in this reaction. Keratinocytes have ICAM-1 adhesive molecules on their surface, which are ligands for the LFA-1 cell receptors of leucocytes. Keratinocytes not only present MHC class II antigens on their surface and produce Il-1 and TNF-α, but also stimulate the inflammatory reaction (3, 4). The release of inflammation mediators and the activation of allergic reaction cells induce epidermal spongiosis and the development of local inflammation. After some time the effector phase is placated by the Treg 1 lymphocytes, which produce Il-10 (5). The antibodies do not play any role in the reaction initiation, which distinguishes contact allergy from other types of allergic reactions.

Oversensitivity to allergens depend on many overlapping factors. On one hand, skin inflammation may cause the development of contact oversensitivity to different antigens. On the other hand, the intolerance of some factors correlates with polyvalent contact allergy shown in patch tests. According to some authors, contact allergy to three or more antigens defines the contact allergy polyvalence. Genetic factors affect this phenomenon (6).

Glucocorticosteroids are drugs commonly used in treating patients suffering from eczema. Synthetic derivatives of adrenal cortex glucocorticosteroids comprise a group of drugs having antiphlogistic, antiproliferative, antiallergic and immunosuppressive properties. Thanks to these properties they constituted a turning point in treating many diseases. They are now being the most often used drugs both in external application, as well as systemically.

Adrenal cortex produces hormones, whose mother substance is cyklopentanoperhydrofenantren, named steroid system. Their traditional name is glucocorticosteroids (gcs), because at first only their effect on glucose transformation was noticed. Thomas Addison described the clinical symptoms of adrenal cortex failure for the first time in 1855. Only in the years 1940-1948 chemical structure was determined. The method of cortisone synthesis was elaborated by an American biochemist Edward Kendall in 1948. In 1949 an American rheumatologist Hench used the synthetically produced cortisone to treat a patient with a rheumatoid joint inflammation (7). It was a 29-year old women immobilized due to intense pains. Two injections of the new drug managed to restore her physical fitness. This spectacular health improvement experienced by her went down to history as a “cortisone miracle”.

In 1950 Edward Kendall, Tadeusz Reichstein and Philip Showalter Hench received a Nobel prize in medicine for their discovery of chemical structure and the function of adrenal cortex hormones and their application in treating rheumatic diseases. For the first time hydrocortisone was used locally for skin diseases treatment in 1952 by Sulzberger and Witten (8). Professor Howard Maibach jokes that the history of dermatopharmacology can be divided into two periods: BC (before corticoids) and AC (after corticoids) (9).

Corticosteroid receptors are located intracellular. They are cytoplasmatic receptors, from which results the concept of their two stages function (two steps model). The first step is creating an active hormone/ /receptor complex, then transferring it to the nucleus and binding with the nuclear chromatin (10). The binding of an active steroid/receptor complex with DNA induces lipocortin-1 synthesis. It is an inflammatory protein from the group of annexines. Lipocortins bind with phospholipids of the cell membranes, disabling A phospholypase to release arachidonic acid from them. As a result, the lipid inflammatory mediators production track breaks (prostaglandin, leukotriene). Glucokorticosteroids restrain the induction of nitric oxide (iNOS) decreasing the inflammatory mediator synthesis this way (11). They also decrease the amount and the activity of mast cells in the skin (12). The most recent studies prove that the active steroid/receptor complex can directly restrain transcriptive factors. The consequence of this process is a reduced expression of adhesive molecules, which blocks the leucocytes migration to the inflammation focus. Also, the proinflammatory cytokines (Il-1, Il-2, Il-6, TFNa) activity and the amount of their receptors decreases.

Gcs currently used in treatment are synthetic derivatives of the adrenal cortex hormones. In comparison to natural compounds they have a stronger anti-inflammatory and immunosuppressive function and produce less unwanted symptoms. For many years the allergy to corticosteroids has been negated, which was caused by their anti-inflammatory properties, which mask the symptoms of contact allergy. The first case of contact allergy to hydrocortisone was recorded in Copenhagen in 1958. Then, 20.000 patients were tested and 0,3% of them had positive results. In Poland, first tests with hydrocortisone were carried out in the years 1980-1981. All of them gave negative results. The first positive results were obtained in 1988 in the Warsaw Dermatological Clinic. The allergy to hydrocortisone was diagnosed in 1% of patients (13).

It may seem that the contact allergy to glucocorticosteroids is much more frequent than it is suspected. Dooms-Goosens proved in his own material that it is similar to the frequency of oversensitivity reaction to PABA and its esters (14). The results of patch tests are often hard to interpret because of the anti-inflammatory properties of gcs. It has been proven, that the allergic

reaction to a steroid has a contact eczema character developing in the IV mechanism. Contact allergy to gcs revealed in skin tests does not always prove the oversensitivity to a steroid molecule. It can be caused by many other substances contained in the substructure, such as emulsions, antioxidants or stabilizers. These compounds cause reactions of a contact nettle rash character. Many other substances added to drugs must be considered, such as antibiotics, antifungal or antiseptics substances, which may also be a reason of developing undesirable allergic reactions.

The comparison of frequency of positive patch tests in sick patients cured with the use of this drugs in the past and the patients who have never used them showed that the frequency of oversensitivity development to gcs increases over time of its use (15).

Clinical observations show that the frequency of contact allergy to gcs constantly increases. There are population differences resulting from the frequency of use of this drug type and from the popularity of particular preparations. Prone to the contact allergy to gcs are mostly patients with chronic inflammatory dermatosis, which include atopic dermatitis, contact eczema and chronic eczema crurum. Patients with those diseases use locally gcs preparations to obtain a remission of lesions. Tests carried out in 13 European centers on 7.238 patients with eczema indicated contact allergy to gcs in 2.6% of the tested patients. Among 189 patients with oversensitivity to gks 21% was diagnosed with AZS, 13% with eczema crurum, 14% with occupational eczema (16). Studies carried in Poland showed a slightly different frequency of contact allergy in long term dermatosis. Comparison studies on 140 patients showed that the positive patch tests occurred in the highest percentage (40%) in chronic venous failure, which indicates an essential therapeutical problem in this group of patients (17). Also, according to Ljubojevic, a limited inflammation, during face skin seborrhea inflammation increases the risk of oversensitivity to gcs development (18).

The possibility of oversensitivity to gcs development after inhalation should be stressed (19). A possibility of allergic reaction development in the place of injection has also been described. In the first case, after the 6th dose of methylprednisolon and in the second case after the 2nd dose of triamcinolon. The oversensitivity to drugs were confirmed by positive epidermal test results in both patients (20). Local application and parenteral gcs application may cause allergic reactions (21). The character of skin lesions after systemic usage of gcs may have a different clinical picture. Anaphylactic reactions and skin lesions (nettle rash) as an immediate allergy and symptoms of delayed reaction (eczema), popular rash and the inflammation of subcutaneous tissue were observed (22-25). In literature there is an accordance stipulating that such reactions after the general use of steroids are not common (26).

Senff described two patients who developed eczema lesions after the use of prednicarbat (Dermatop®) as a salve and a cream (27). Lobular tests confirmed oversensitivity to this compound. No cross reaction with other drugs of this type has been confirmed. The authors stress that when there is no improvement after the application of gcs, especially after inflammation intensification, the oversensitivity to steroids must always be considered.

One of the first publications objectively confirming the possibility of causing allergic reaction to gcs was a Laurem's & co. report, in which the authors studied the phenotype of cellular infiltration in 13 patients, who had taken a cutting form the place of positive patch test on steroids with the use of avidin-biotin complex technique (28). Cell kinetic reaction caused by gcs with the oversensitivity reaction (of cell type) caused by other antigens were compared. However, in both cases a decrease of dendrite cells (of both types) was observed. In case of steroids, the reaction occurred after a longer time than in a reaction not connected with gcs. A smaller amount of T lymphocytes was observed. The authors justify it by a modeling effect of steroids in delayed allergic reaction.

A golden standard in the contact allergy diagnosis are epidermis patch tests. Today they are highly advanced. The corticosteroids division into 4 types was created due to their chemical structure (tab. 1). Knowledge of this classification is helpful while determining possible cross reactions, which are the cause of allergic reaction to a steroid, which has not been applied earlier. Cross reactions are also causes of oversensitivity simultaneously to few drugs containing gcs. On the basis of analysis of 1188 patients, who were suspected to have a bad steroids tolerance, 127 patients had a positive reaction to one of the compounds. In 56 cases there occurred the oversensitivity to a few drugs simultaneously (29).

"Screening allergens" for a particular drug types were determined in the studies of contact allergy reactions to gcs. Tixocortol pivalate is considered as a sensitive and specific allergy marker to hydrocortisone (A group) (30). Triamcinolone acetonide and budezonid for B group, hydrocortisone butyral for D group. The C group, whose diagnostic allergens are dexamethasone and desoxymethasone phosphate was considered to be the least likely to cause contact allergy. The studies proved that the positive reaction to tixocortol pivalate was shown in 48%, the addition of budesonide increased the detectability to 68%. Other studies showed even a higher percentage (up till 90%) (31, 32).

The development of contact oversensitivity reaction is also affected by age. Children are more likely to develop a generalized allergic reaction to the locally applied gcs due to a higher relation of their total surface to their body mass (34).

A technical aspect has a huge role in assessing the factor causing allergic reactions, including allergy to steroids. It regards all the stages of contact patch tests. It has been reported that the percentage of positive

Table 1. Structural classification of corticosteroids (33).

Class A	Hydrocortisone, Methyloprednisolone Tixocortol pivalate
Class B	Triamcinolone acetonide Triamcinolone Fluocinolone acetonide Fluocinolone Budesonide Amcinonide
Class C	Betamethasone Dexamethasone Desoxymethasone Fluocortolone Flumetasone pivalate
Class D1	17 – betamethasone valerate 17, 21 – betamethasone dipropionate 17 – clobetasone butyrate 17 – clobetasone propionate Momethasone Flutikasone
Class D2	17 – Hydrocortisone butyrate Hydrocortisone buteprate Aceponate Prednicarbate Methyloprednisolone

Table 2. European topical corticosteroids classification according to potency.

Class IV. Very potent	Clobetasol propionate 0.05% Fluocinolone acetonide 0.2% Halcynonid 0.1%
Class III. Potent	Fluticasone propionate 0.05% Betamethasone dipropionate 0.05% Triamcinolone acetonide 0.1% Fluocinolone acetonide 0.1% Amcinonide 0.1% Desonide 0.05% Budesonide 0.025% Fluticasone propionate 0.05% Betamethasone valerate 0.1%
Class II. Moderate	Betamethasone dipropionate 0.05% Triamcinolone acetonide 0.04% Betamethasone valerate 0.025% Flumetasone 0.02%
Class I. Mild	Hydrocortisone 0.5%, 0.1% Dexamethasone 0.1%, 0.2% Methyloprednisolone 0.25% Fluocinolone acetonide 0.0025%

results of epidermal tests increases together with the concentration and potency of applied allergen (35). According to the European classification, topical glucocorticoids are subdivided into four groups by the potency of their therapeutic effect: group I includes the least potent agents and group IV the most potent ones (tab. 2).

A certain role has also the amount of simultaneously applied allergens, which affects the increase of positive result percentage.

There are some discrepancies regarding the assessment time of test results, especially in regard of delayed reactions. Some of the authors make readings during the second, third and sixth day, others during the third, fourth and seventh day. The study on 306 patients, on whom tests with tixokortol pivalate and triamicinolone acetonide were carried out, had negative results in most cases (36). 17 patients developed positive reactions only during the 5th day, in 13 of them the reaction remained also in the 7th day. It confirms that a different time in regard of delayed reactions is possible. Similarly, Ljubojevic obtained false negative results in 5 out of 100 patients (37). In one of them only the 2nd reading shoved positive reaction. Others developed allergic reactions in the place of allergen application during the 7th day. According to Isaksson about 30% of contact reactions to gcs develops only during the 7th day (38). Reading omission during this time increases the percentage of false negative reactions.

The possibility of negative epidermal test in patients reporting the intensification of skin lesions after their application, gcs must also be considered in the assessment of oversensitivity. In such cases it is advisable to carry out a test with a commercial preparation. Clinical studies show that commercial preparations may contain compounds, which increase the penetration and bioavailability of allergens (39).

Allergic reactions should be distinguished from irritation, the latter is characterized by a gradual regression over time (48-72 hours) (40).

Diagnosed contact allergy may significantly improve the life quality and decrease the symptoms as the patient will be able to avoid the exposure to hapten, the cause of oversensitivity. Glucocorticosteroid allergy is so interesting and surprising phenomenon that it was named as the allergen of the year 2005.

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