

ANAPHYLAXIS INDUCED BY INTRAMUSCULAR BETAMETHASONE DISODIUM PHOSPHATE: REFLECTIONS ON A CLINICAL CASE

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Glucocorticoids could be responsible for allergic symptoms correlated to an Ig-E mediated hypersensitivity mechanism. We describe the case of an anaphylactic reaction in a professional nurse, occurring after an intramuscular administration of Betamethasone. After performing skin prick tests, intramuscular tests and patch tests we concluded that the patient had Ig-E mediated sensitization. She was prescribed oral Prednisone and Deflazacort and shows good tolerance of these drugs. This demonstrates that in these patients it is possible to administrate glucocorticoids without the changes in the sites indicated by Wilkinson. Nevertheless, our patient showed a negative allergy test for Dexamethasone disodium phosphate, and in those patients sensitized to fluorinated glucocorticoids, tolerance to other glucocorticoids is not so easily predictable as in patients with hypersensitivity to first generation steroids or in corticosteroid contact dermatitis, according to the four patterns of cross-reactivity proposed by Coopman and Dooms-Goossens.

Immediate hypersensitivity and IgE-mediated reactions to systemic Corticosteroids (CSs) are considered rare adverse reactions, despite reports in literature (1-2). Recently, improvements of laboratory methods have made it possible to isolate specific IgE for CSs (1), confirming the allergic pathogenesis of the numerous adverse reactions described (2-3). Hydrocortisone and methylprednisolone succinate esters (2) are the most frequent substances triggering immediate type adverse reactions, while halogenated CSs are rarely involved (2-3).

We describe the case of an anaphylactic reaction in a professional nurse, occurring after an intramuscular administration of Betamethasone

sodium phosphate.

Clinical case

The patient is a 57-year-old professional nurse, with a clinical history of previous hypersensitivity reactions to an unspecified non-steroidal anti-inflammatory drug (NSAIDs) with dizziness, asthenia, vomiting and hypotension. After this episode she had urticaria and angioedema after taking Pyroxicam, and referred a vasomotor rhinitis, treated with various topical CSs (above all, mometasone furoate and flunisolide).

In addition, the patient had a slipped disk at the level of L3-L4 and L4-L5 and was treated with

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Betamethasone disodium phosphate (Bentelan 4 mg) fl i.m. After the first dose of this drug the patient developed generalized urticaria with intense itching and asthenia. In the emergency ward her symptoms worsened, with hypotension (PA 90/60 mmHg) and dyspnea, and she was promptly treated with adrenaline and plasma-expanders. Hydrocortisone Hemisuccinate (Solucortef) 300 mg i.v. was administered, resulting in complete resolution. The patient was hospitalized and submitted to allergological evaluations. From the clinical history, a heavy consumption of topical CSs emerged, used both for the vasomotor rhinitis and for some recent surgical scars (prevention of keloids with betamethasone valerate ointment). At the same time, the patient referred tolerance of sparkling white wines, without itching, urticaria or rhinorrhea, thus excluding any responsibility in the genesis of the reaction of sodium bisulphite, contained as a preservative in the Betamethasone vials.

MATERIALS AND METHODS

Patch tests with corticosteroid molecules (provided by various pharmaceutical companies), as shown in Table I, were carried out with Van der Bend Chambers. They were removed after 3 days and read on days 4, 7 and 10.

On the 10th day the patient was submitted to Skin Prick Tests (SPT) and Intradermal tests with various systemic CSs (commercial molecules). Intradermal tests were carried out by administering 0.05 ml of each glucocorticoid diluted in 0.9% saline (with the concentration reported in Table I) every 30 minutes. If SPT or intradermal test was obviously positive, we stopped the successive skin test with the responsible CS. Further readings of intradermal tests on 2nd, 3rd and 4th days were planned to investigate the contemporary presence of a delayed hypersensitivity. Saline solution and histamine dihydrochloride 0.1 mg/ml were used as negative and positive control respectively, and skin tests and their readings were performed according to the recommended guidelines of the European Network for Drug Allergy (ENDA) (4). As negative control two operators were subjected to the same skin tests protocol illustrated in Table I. They were not-atopic and did not suffer from drug allergy or corticosteroids hypersensitivity.

Moreover, the patient was submitted to oral tolerance tests (OTT) with oral Prednisone according to the following scheme: 5 mg - 10 mg - 15 mg - 20 mg for a total dose of 50 mg. The tests were well tolerated.

Another OTT was carried out with Deflazacort drops

with the same method: 5 drops - 10 - 15 - 30 drops equal to a final dose of 60 mg. The patient tolerated this drug also, but refused other OTT with Dexamethasone sodium-phosphate drops and triamcinolone 8 mg tablets.

The OTT were performed in the Intensive Care Unit after having obtained written informed consent from the patient. After day 17 from the allergic reaction, the total IgE resulted elevated (250 kU/l, Pharmacia CAP System, Uppsala, Sweden). In addition, dosages of specific IgE to latex were performed (Pharmacia CAP System, Uppsala, Sweden).

RESULTS

Patch Tests to Corticosteroids resulted negative as did the dosage of specific IgE to latex. Skin Prick Test and Intradermal test elicited a positive reaction towards betamethasone and methylprednisolone at the immediate reading, as shown in Table I, while no corticosteroid elicited any reactions at the following delayed readings. On the contrary, skin tests resulted negative in the control group. No patch tested corticosteroid elicited any reactions at the delayed readings. OCT gave negative results without eliciting any immediate or delayed-type clinical manifestations in the patient who showed only high values of total IgE (250 kU/l - v.n. 100 kU/l). Relevance of specific IgE to betamethasone was not investigated by a radio-allergosorben-test (RAST).

DISCUSSION

Known risk factors for allergic reactions to CSs are: 1) bronchial asthma, 2) hypersensitivity to acetylsalicylic acid (ASA) and to NSAIDs, 3) the intravenous administration route, 4) high dosages and 5) the presence of a kidney disease or renal transplantation (2). In addition, other risk factors have been suggested: 1) the presence of an autoimmune disease; 2) the presence of a chronic skin disease with topical use of CSs and consequent skin absorption; 3) the presence of an underestimated contact dermatitis to topical CSs (3).

Our patient did not remember having previously taken fluorinated systemic CS but she had used topical halogenated CSs for both health (5) and professional reasons (6), thus triggering a sensitization through the cutaneous route, which involves a preferential IgE-mediated mechanism

Table I. *Diagnostic skin tests with corticosteroids.*

CORTICOSTEROIDS	SKIN PRICK TESTS	INTRADERMAL TESTS
Methylprednisolone succinate (Solumedrol)	20 mg/mL: positive	/
Hydrocortisone succinate (Soluortef)	100 mg/mL: negative	0.1 mg/mL – 1 mg/mL – 10mg/mL: negative
Betamethasone sodium-phosphates	4 mg/mL: positive	0.4 mg/mL: positive (Bentelan)
Dexamethasone sodium-phosphate (Soldesan)	4 mg/mL: negative	0.4 mg/mL – 4 mg/mL: negative
Triamcinolone acetonide (Kenacort Retard)	40 mg/mL: negative	0.4 mg/mL – 4 mg/mL – 40 mg/mL: negative
Histamine 1%	++++	
Saline 0,9%	negative	
PATCH TESTS		
- Tixocortol Pivalate 1% in vaseline	negative	
- Budesonide 0.1% in vaseline	“	“
- Betamethasone valerate 1% in alcoholic solution	“	“
- Clobetasol propionate 1% in alcoholic solution	“	“

rather than a cell-mediated one.

Few reports have been made in literature of allergic type reactions immediately after the administration of Betamethasone (7-9), and no specific IgE have yet been identified *in vitro* either to Betamethasone or to other fluorinated CSs, while lymphocytes T CD4+ for Betamethasone were isolated in the blood of a patient who manifested a generalized urticarioid eruption 24 hours after the administration of the steroid (10).

Maddin was the first to describe the onset of urticaria following the application of a cream with a betamethasone base; intramuscular administration of betamethasone determined the appearance of the urticaria after 10 minutes (7). Recently, Ehret described the case of a patient in which intra-articular administration to the right knee of 14 mg of an association of two Betamethasone salts (sodium phosphate and propionate) caused the onset of asthenia, dyspnea, a feeling of heat and facial

erythema, together with diffuse bone pain. The symptoms spontaneously regressed within an hour but manifested again after an intramuscular challenge test with 3.5 mg of the same drug (8). A positive intradermal reaction with an unspecified dilution of betamethasone was obtained, determining the appearance of a wheal measuring 6 mm in diameter. Instead, the patient tolerated Methylprednisolone acetate, that is a non-halogenated GC. A most recent case report describes an anaphylaxis due to betamethasone sodium phosphate during anaesthesia in a 58 year-old female patient. The dosage which elicited anaphylactic reaction was 2 mg injected intravenously, while skin tests, performed at unreported concentrations, was positive for the steroid and negative for preservatives (9). The authors did not mention alternative steroid molecules tolerated by the patient.

Dewachter suggests that immediate type adverse reactions to intra-articular betamethasone can also

be attributed to a different causal agent in the steroid: polyethyleneglycol or macrogol 4000 (11).

PEG is contained in the formulation of Methylprednisolone acetate (8), while it is not present in the formulation of the succinate (11), therefore the allergic reaction to betamethasone reported by Ehret (8) appears actually to be a reaction to the steroid itself. Our patient had positive cutaneous allergological reactions not only to Betamethasone disodium phosphate, which does not contain PEG, but also to Methylprednisolone sodium succinate, i.e. a steroid formulation lacking PEG and sulphites. Furthermore, the clinical history of the patient was not suggestive for sulphite hypersensitivity, and specific IgE to latex resulted to be negative.

Betamethasone has an atom of Fluorine in position alpha on C9 and a methyl group - CH₃ in position beta on C16, while MP has only a methyl group in alpha position on C6 (12), therefore the existing structural differences between the 2 steroid molecules should modify the allergenicity, making the drug more easily tolerated.

Besides the well known subdivision of topical corticosteroids into 4 allergenic classes proposed by Coopman and Dooms-Goossens (13), Wilkinson has suggested that the immunodominant sites that influence the corticosteroids allergenic cross-reactivity are not only the positions C16/C17, but also C6/C9 (14).

Fluorinated GCs are metabolised by passing through the liver, so the structural formula could be modified also, as it occurs at a cutaneous level for topical CSs (15).

Pharmacokinetic studies of triamcinolone acetonide, that is a 2nd generation fluorinated systemic CS, have, in fact, demonstrated the presence in the urine of dogs and monkeys of various metabolites, including 5% of 6-alpha-hydroxy-triamcinolone (16).

Paradoxically, the patient we examined also had negative skin tests to Dexamethasone disodium phosphate, that is a CS with a similar structural formula to that of Betamethasone except that the methyl group CH₃ on C16 is positioned on alpha instead of beta. Moreover, on the Italian market, dexamethasone vials essentially contain the same preservatives as betamethasone. The patient refused to undergo an oral challenge test with dexamethasone so we were unable to clearly confirm full tolerance.

The lack of cross-reactivity between betamethasone and dexamethasone in the course of immediate type allergic reactions was recently described (17), unlike that which occurs in cases of cell-mediated delayed type reactions (18).

The experimental administration of a conjugated cortisol-albumin in mice caused the formation of selective anticortisol antibodies toward a specific steroid isomer (19), suggesting a selective humoral response. It is quite easy to find an alternative CS molecule in patients with immediate type reaction to succinate salts of hydrocortisone, prednisolone and methylprednisolone (20-21). On the contrary, the more changes are present on the steroid molecule to which the patient is sensitized, the more difficult it is to find an alternative CS (22).

CONCLUSION

We suggest that in the case of immediate type reactions to 2nd generation corticosteroid molecules as betamethasone, triamcinolone, dexamethasone and paramethasone, skin tests and oral challenge test should be performed. In fact cross-sensitivity is far different from the four group classification proposed by Coopman-Dooms-Goosen in cell-mediated reactions, therefore it is not so easily predictable.

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