Reazioni avverse ai corticosteroidi

12 aprile 2013
ADVERSE DRUG REACTIONS

Type A
80% of all side effects

Type B
15-20% of all side effects

Idiosyncratic reactions

Hypersensitivity reactions

Immune mediated
(drug allergy)

Non immune mediated
“pseudoallergy”

Predictable, strictly dose dependent
Pharmacological side effects
(e.g. gastrointestinal bleeding under treatment with NSAID, or bradycardia with β blocker treatment)

Not predictable, usually not dose dependent, sometimes reactions to very small amounts

Hypersensitivity reactions

Immediate reactions
Are those occurring within 1 h after the last drug administration

Nonimmediate reactions
Are those occurring more than 1 h after the last drug administration
i corticosteroidi sono i farmaci più frequentemente usati per trattare le malattie allergiche

paradossalmente, sono stati riportati casi di reazioni di ipersensibilità, in alcuni casi anche reazioni con pericolo per la vita

Rachid R JACI 2011
Corticosteroids are low molecular weight compounds that act as haptens and need to bind to proteins to induce a hypersensitivity reaction.

Bundgaard in 1980 suggested that corticosteroids were degraded to a corticosteroid glyoxol that then reacts with arginine molecules of proteins to form the complete antigen.

Somministrazione topica (2.9–6%)
- nonfluorurati (come idrocortisone e budesonide)

- la reazione può essere dovuta ad altri costituenti delle creme, (come neomicina o cetylsteryl alcohol)

Somministrazione sistemica (<1%)
- metilprednisolone e idrocortisone

- in alcuni casi può essere indotta da Sali (come il succinato)

- raramente può essere indotta da certi diluenti come la carbossimetilcellulosa o metabisolfito
Somministrazione topica

- dopo somministrazione topica di corticosteroidi sulla pelle
  - lesioni eczematose
    (che non migliorano dopo somministrazione di corticosteroide topico)

- dopo somministrazione topica di corticosteroidi bronchiale o nasale
  - reazioni avverse locali
    - dermatiti da contatto, prurito, congestione nasale, eritema e tosse secca

- reazioni avverse sistemiche
  - lesioni eczematose (in particolare al volto), esantema e orticaria (la budesonide è quello più frequentemente coinvolto)
Patch test positivity to corticosteroid has been reported in two asthmatic patients with generalized cutaneous symptoms after receiving fluticasone or budesonide.
Are reactions to inhaled corticosteroid immunemediated?

A patient who developed a generalized exanthema 8 h after inhalation of nasal budesonide

- The patch test was positive with budesonide
- The skin biopsy showed:
  - A perivascular mononuclear cell infiltrate, with the presence of CD4+, memory cells (CD45RO+), expression of the homing receptor CLA
  - The lymphocyte transformation test was positive to budesonide,
  - Increasing in the presence of dendritic cells
- Lymphocyte trasformation test was positive to budesonide

Lopez S et al. Journal of Investigative Dermatology 2010
Cross-reactivity

Cross-reattività

- alta fra i corticosteroidi di ogni Gruppo
- alta fra il Gruppo D2 e i Gruppi A e B
- bassa del Gruppo D1 con gli altri Gruppi

Utile nella valutazione delle reazioni indotte dalla somministrazione topica dei corticosteroidi, non accettata in tutto il mondo

The patch-test results obtained with 66 corticosteroid molecules in 315 previously sensitized subjects were analysed and correlated with modelling and clustering in function of the electrostatic and steric fields of these molecules.
Esso quindi indica la forza delle relazioni esistenti tra due elementi in base alla distanza che intercorre tra l'origine (0) e la linea verticale più vicina che connette le linee orizzontali corrispondenti ai due elementi considerati.

Per capire quale sia la relazione tra due elementi, tracciate un percorso da uno dei due all'altro, seguendo i rami del diagramma ad albero e scegliendo la strada più breve. La distanza dall'origine alla linea verticale più esterna toccata dal percorso rappresenta il grado di somiglianza tra i due elementi.
This study demonstrates the existence of two subgroups of patients with probably different areas of immune recognition:

- **patients who react to molecules from one unique group**

- **patients who may react to the entire spectrum of corticosteroids**

The latter population probably presents with a powerful **enzymatic hydrolysis system** or recognizes the **global skeleton** of the steroid molecules rather than particular substitutions.

*Isaksson M et al. Contact Dermatitis 2003*

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**Table: Cross-reactivity**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
<td>No C8-methyl substitution</td>
<td>C8/C9 cis keto-ene structure</td>
<td>C8-methyl substitution</td>
</tr>
<tr>
<td></td>
<td>No halogenation (in most cases)</td>
<td>Halogenation (in most cases except*)</td>
<td>Halogenation (except*)</td>
</tr>
<tr>
<td><strong>Indicative structure</strong></td>
<td>![Structure A]</td>
<td>![Structure B]</td>
<td>![Structure C]</td>
</tr>
</tbody>
</table>

*Baeck M et al. Allergy 2011*
- **Patch test**
  - with the corticosteroid markers (tixocortol pivalate 0.1% pet., budesonide 0.01% pet., and hydrocortisone 17-butyrate 1% ethanol)
  - 0.1% (instead 1%)
  - CS preparations used by the patient, along with all other ingredients, including additives and preservatives
  - late readings between 3 and 7 days are necessary (anti-inflammatory properties of CSs)

- **Intradermal tests with late readings**
  - should **not** be performed routinely (risk of atrophy)
  - only in particular cases (suggestive history but false-negative patch test results)
  - diluted 30%, 10% and 1% in saline (no atrophy has been observed)

- **Biological *in vitro tests***: research tools

*Baek M et al. Contact Dermatitis 2011*
Somministrazione sistemica
(orale, parenterale e/o intraleionale)
Reazioni immediate

- sintomi:
  - orticaria localizzata o generalizzata
  - angioedema,
  - broncospasmo
  - ipotensione
  - shock anafilattico

- farmaci maggiormente coinvolti:
  - metilprednisolone
  - idrocortisone
<table>
<thead>
<tr>
<th>Time</th>
<th>Presentation / activity</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00</td>
<td>Task Force 1: Drug Allergy and Mast Cell Disorders</td>
<td>P. Bonadonna</td>
</tr>
<tr>
<td>09:45</td>
<td>Task Force 2: Drug Hypersensitivity in Children</td>
<td>E.M. Gomes, Porto</td>
</tr>
<tr>
<td>10:00</td>
<td>Coffee break</td>
<td>Entrance hall in front of auditorium 1 &amp; 2, 2nd floor</td>
</tr>
<tr>
<td>11:00</td>
<td>Task Force 3: Allergy Passport</td>
<td>K. Brockow, München</td>
</tr>
<tr>
<td>11:45</td>
<td>Task Force 4: Skin tests</td>
<td>K. Brockow, München</td>
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<tr>
<td>12:00</td>
<td>Lunch</td>
<td>Hospital restaurant</td>
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<tr>
<td>13:00</td>
<td>Symposium: Clinical Problems in Drug Hypersensitivity</td>
<td></td>
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<tr>
<td>14:00</td>
<td>IgE-mediated anaphylactic reaction caused by beta 1a interferon (15')</td>
<td>G. Cortellini, Rimini</td>
</tr>
<tr>
<td>14:15</td>
<td>Anaphylactic shock from methylprednisolone succinate (15')</td>
<td>M.B. Bilò, Ancona / A. Bircher, Basel</td>
</tr>
<tr>
<td>14:30</td>
<td>CoLD in children (16')</td>
<td>E.M. Gomes, Porto</td>
</tr>
<tr>
<td>14:45</td>
<td>Ethylene oxide sensitization (30')</td>
<td>L. Hese Garvey, Friedenbürg</td>
</tr>
<tr>
<td>15:00</td>
<td>Anacavir skin reactivity in abacavir naïve HLA-B*1501 carriers (30')</td>
<td>B. Schindler, Bern</td>
</tr>
</tbody>
</table>

**14:15-14:30** Anaphylactic shock from methylprednisolone succinate (15')

M.B. Bilò, Ancona / A. Bircher, Basel
CASE 1

Female, 50 y.o.

Allergic rhinoconjunctivitis due to grass pollen and house dust mites; no asthma

No history of previous drug hypersensitivity reactions

Previous tolerance of oral steroids (betametasone)

12-16-2010:
• During hospitalization (in another hospital) for suspected multiple sclerosis she developed an **anaphylactic shock** (PA 50/35 mmHg) within few minutes after an intravenous injection of methylprednisolone sodium hemisuccinate (and 30’ after one table of pantoprazol).

• Diagnosis was made by an Anaesthestist.

• The patient recovered from the episode without sequelae.

• No measurement of serum tryptase level was made in the acute phase.
CASE 2

Female, 54 y.o., nurse (an already known patient)
No atopy.

Anaphylactic shock after a yellow jacket sting (2002)
On VIT.

No history of previous drug hypersensitivity reactions

Previous oral tolerance of prednisone and betametasone
Recent knee infiltration with methylprednisolone acetate: tolerated

15-05-2012:

• Because of a recent diagnosis of an uterus cancer, she fixed a TC with CM.
• Within few minutes after an intravenous injection of methylprednisolone sodium hemisuccinate as premedication for contrast medium use (she had an anaphylactic shock to stings!!!!!), she developed an anaphylactic reaction (sneezing and nasal obstruction, cough, dispnoea, urticaria, abdominal pain).
• The patient recovered from the episode without sequelae.
• No measurement of serum tryptase level was made in the acute phase.
Intradermal tests:
- methylprednisolone s.h. positive,
- prednisolone s.h., hydrocortisone s.p., dexamethasone s.p., and deflazacort. negative

Single-blind, placebo-controlled challenge tests (SBPCCT): prednisolone s.h., hydrocortisone s.p., dexamethasone s.p., and deflazacort negative

Challenge tests with excipients of methylprednisolone s.h. were negative

Oral challenge test with methylprednisolone, with negative result.

Methylprednisolone s.h. (intramuscular) positive (the patient developed nasal blockage, rhinorrhea, dry cough, and macular exanthema on her neck and abdomen)

Facial pruritus, angioedema of the lips and face, and hives in a 26-year-old woman (allergic rhinoconjunctivitis and mild and intermittent asthma, bronchospasm secondary to airway infection)

10 min after intramuscular dose of methylprednisolone sodium hemisuccinate (s.h.)
Sali formati neutralizzando l'acido succinico sono chiamati succinati. Un esempio è il sodio succinato, un bianco, sale solubile in acqua in order to make corticosteroid water soluble for intravenous application they are coupled in C21 to ester (succinate ester).
Systemic anaphylactic reactions to intravenous administration of corticosteroids occurred in 7 adult with severe atopic asthmatics with previous exposure to parenteral corticosteroids, irrespective of age and gender.

In all cases, anaphylactic reactions were induced following intravenous administration of succinate-containing corticosteroid preparations, i.e. hydrocortisone and methylprednisolone.

Administration of phosphate-containing corticosteroids, i.e. dexamethasone and betamethasone, was safe and resulted in a resolution of anaphylactic symptoms.

Nakamura H Respiration 2002
H.J. is a 20-year-old man

B.B. is an 18-year-old man,

facial oedema after an intravenous injection of 120 mg of Solumedrol (methylprednisolone sodium succinate)

One month later

SPT at 10 mg/ml Solumedrol was positive (not knowing the positive predictive value)

I.D.T., performed with Solumedrol, resulted positive at the concentration of 1 mg/ml

challenge with Solumedrol obtained conjunctivitis, oedema of the eyelids, urticaria and bronchospasm beginning of the test at the total cumulative dose of 6.1 mg of drug

oral challenge with Medrol (methylprednisolone without ester) which produced negative results

Table 1. List of drugs and drug galenic forms frequently present as succinate esters

<table>
<thead>
<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>Erythromycin</td>
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<tr>
<td>Amoxicillin</td>
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<tr>
<td>Amprenavir</td>
</tr>
<tr>
<td>Bismuth</td>
</tr>
<tr>
<td>Cibenzoline</td>
</tr>
<tr>
<td>Doxylamine</td>
</tr>
<tr>
<td>Fosfomycin</td>
</tr>
<tr>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>Loxapine</td>
</tr>
<tr>
<td>Methylphenidate</td>
</tr>
<tr>
<td><strong>Methylprednisolone</strong></td>
</tr>
<tr>
<td>Metoprolol</td>
</tr>
<tr>
<td>Octenidine</td>
</tr>
<tr>
<td>Succinylcholine</td>
</tr>
<tr>
<td>Sumatriptan</td>
</tr>
<tr>
<td>Verapamil</td>
</tr>
</tbody>
</table>

Caimmi S et al. Allergy 2008
Hypersensitivity to systemic corticosteroids in aspirin-sensitive patients with asthma

Hypersensitivity to NSAIDs in patients with asthma appears to be sporadically associated with idiosyncratic reaction to hydrocortisone. Glück J et al. Pol Arch Med Wewn 2009

Asevere airflow obstruction was described in 2 aspirin-intolerant asthmatic (AIA) patients within a few minutes after injection of 100 or 200 mg of hydrocortisone; one of the reactions was almost fatal. Partridge MR et al. Br Med J 1978

In 3 of 11 AIA patients, dyspnea and fall in spirometric values beginning 3 to 5 minutes after intravenous injection of 100 mg of hydrocortisone, but not after saline or hydrocortisone solvent, was reported. Dajani BM et al. J Allergy Clin Immunol 1981

Bronchospasm and naso-ocular reaction to hydrocortisone succinate in 1 of 45 challenged AIA subjects, who also reacted to methylprednisolone succinate. Aspirin desensitization did not prevent these reactions. Feigenbaum BA et al. J Allergy Clin Immunol 1995

In 31 AIA patients, a systematic study of the effects of intravenous bolus of 300 mg of hydrocortisone revealed a significant fall in FEV1 5 minutes after the injection. Only 3 of these 31 patients displayed clinical sings of bronchoconstriction. Szczeklik A et al. J Allergy Clin Immunol 1985

Bronchoconstriction could be precipitated by succinate salts of both hydrocortisone and methylprednisolone, but not by the phosphate salts. It is, therefore, advisable to use other steroids in AIA patients, preferably nonsuccinate salts. Szczeklik A JACI 2011
- Skin tests
  - prick ‘as is’ and
  - intradermal tests at progressively higher concentrations (1/1000, 1/100 and then 1/10 of a saline dilution of the ‘as is’ corticosteroid preparation), within 1–3 months following this adverse event

- exclude allergic reactions to additives/preservatives (such as carboxymethylcellulose or macrogol)

- Biological in vitro tests:
  - Tryptase levels (acute phase)
  - Specific IgE
  - Basophil activation test

- Oral provocation tests (remain the gold standard for confirming or refuting the patient’s hypersensitivity)
Cross-reactivity

- the classification and cross-reaction patterns observed with delayed reactions, particularly allergic contact dermatitis, do not seem to be fully useful here

- in many sensitized individuals, allergic reactions to hydrocortisone and methylprednisolone have been observed without cross-reactivity to other group 1 molecules such as prednisone and prednisolone esters of CSs, without cross-reactivity to non-esterified molecules, or with those with other ester substitutions, that is, phosphate or acetate

Baeck M et al. Contact Dermatitis 2011
Somministrazione sistemica
(orale, parenterale e/o intralesionale)

**Reazioni non immediate**

- non frequenti e di solito lievi

- orticaria ritardata o esantema maculopapulare

- Sindrome di Stevens–Jonhson, Necrolisi Epidermica Tossica o Pustolosi esantematica acuta generalizzata (segnalazioni aneddotiche)
38 individuals (mainly women), developed delayed reactions after systemic corticosteroid administration.

Skin (prick and intradermal) and patch testing just two were positive, to dexamethasone and betamethasone.

Controlled administration
Six of the 38 patients refused to be tested. Of the remaining 32 patients, 21 were finally diagnosed as being allergic to CS.

### Drugs involved

<table>
<thead>
<tr>
<th>Drug involved</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone</td>
<td>66%</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>24%</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>10%</td>
</tr>
</tbody>
</table>

Table 1. Drug involved, clinical symptoms and time interval in 21 subjects with an allergic reaction after controlled administration of corticosteroids.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Drug involved</th>
<th>DPT</th>
<th>Symptoms</th>
<th>Time interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Betamethasone</td>
<td>Bet; Bet; MP-S</td>
<td>Urticaria</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>Dexamethasone</td>
<td>Bet; Bet; MP-S</td>
<td>Exanthema</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>Betamethasone</td>
<td>Bet; Bet; MP-S</td>
<td>Urticaria</td>
<td>15</td>
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<tr>
<td>4</td>
<td>Betamethasone</td>
<td>Bet; Bet; MP-S</td>
<td>Urticaria</td>
<td>24</td>
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<tr>
<td>5</td>
<td>Dexamethasone</td>
<td>Bet; Bet; MP-S</td>
<td>Urticaria</td>
<td>5</td>
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<tr>
<td>6</td>
<td>Dexamethasone</td>
<td>Bet; Bet; MP-S</td>
<td>Exanthema</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>Triamcinolone</td>
<td>Bet; Bet; MP-S</td>
<td>Urticaria</td>
<td>6</td>
</tr>
</tbody>
</table>

DPT: drug provocation test; Bet, betamethasone; Dex, dexamethasone; MP-S, methylprednisolone succinate; P, prednisone; AE, angioedema.

Low sensitivity of skin testing.

Padial A et al. Allergy 2005
Patients with contact allergy to hydrocortisone can develop cutaneous reactions after oral administration of hydrocortisone and cortisolo.

Patients with contact hypersensitivity to hydrocortysone-17-butyrate can tolerate other compounds.

16 subjects (out of 315 with CS delayed-type hypersensitivity) presented with allergic manifestations due to systemic administration of corticosteroids.

**Conclusion**

5% of the corticosteroid-allergic patients presented with generalized eczematous or maculopapular eruptions following systemic exposure to molecules to which they had previously tested positively. Most of the reactions observed are ‘systemic contact dermatitis’ due to oral or parenteral reexposure of sensitized individuals with the respective corticosteroids previously applied topically.

Baeck M et al. Allergy 2012
sebbene rare, le reazioni allergiche ai corticosteroidi esistono

un meccanismo immunologico, dovuto a IgE o cellule T è stato dimostrato

test cutanei ed in vitro possono aiutare nella diagnosi (sensibilità, specificità e valore predittivo positivo o negativo?)

in molti casi il test di provocazione è ancora necessario per confermare la diagnosi
Grazie per l’attenzione
<table>
<thead>
<tr>
<th>Name</th>
<th>Strength/Formula</th>
<th>Strength/Formula</th>
<th>Strength/Formula</th>
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<tbody>
<tr>
<td>Flebocortid Solucort</td>
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<td>Rapicort Cortop</td>
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<tr>
<td>Urbason Solumedrol</td>
<td>Idrocortisone emisuccinato sodico (100mg/2ml)</td>
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<td>Metilbetasone Supresol</td>
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<td>Depomedrol</td>
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<td>Kenacort Triacort</td>
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<td>Triamcinolone acetonide</td>
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<td>Triamvirgi</td>
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<td>Betametasone fosfato disodico (4mg/2ml)</td>
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<td>Betametasone</td>
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<td>Desametasone 21 fosfato sodico</td>
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<td>Decadron Soldesam</td>
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<td>Capital Desametasone</td>
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<td>Prick</td>
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<td>I.D.</td>
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