Corticosteroids delayed hypersensitivity: diagnostic and cross-reactivity

Marie Baeck
‘Paradoxical’ condition

Treatment of inflammatory and allergic diseases

Sometimes responsible for immediate or delayed allergic hypersensitivity reactions (IAHRs – DAHRs)
1. Diagnostic

2. Classification and cross-reactions

3. Practical guidelines
Diagnosing corticosteroids allergy: a challenge for clinicians!

Clinical signs are usually minor, with an atypical chronology

Skin-test results difficult to interpret
No response or worsening following CS treatment of a cortico-sensitive dermatitis
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Clinical presentation dominated by ‘classical’ side effects of CSs
‘edge effect’
8e Congrès Francophone d'Allergologie

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ACD following ocular use of dexamethasone (ointment) and dexamethasone Na-phosphate (eyedrops)
ACD following inhalation of CSs (budesonide)
Generalized eruption
Indisputable value of patch testing

With **ethanol** as vehicle

Markers: Tixocortol pivalate, budesonide, hydrocortisone 17-butyrate
(detection of 92.5% of the CS-sensitized patients)

Importance of testing with the specific CSs used by the patient!

Concentration: **low!**
Readings pitfalls...

Interest of late readings, day 6 or 7, or even later

Particular effects related to CSs:

- ’Edge effect’
- Vasoconstriction
- Vasodilation
Prick or intradermal tests with late readings?

ID tests with late readings should NOT be routinely performed:

– Important risk of atrophy, particularly with CSs in suspension (Diprophan®, Kenacort®, Pulmicort®) >= solutions
Prick tests | ID tests | Patch tests

'as is'
30%
10%
1%

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Skin atrophy: Diprophos®‘as is’ and diluted 30%, 10%
AMBULANCE

MAXIME

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1. Diagnostic

2. Classification and cross-reactions

3. Practical guidelines
Many different corticosteroids: a same basic structure

Three rings of 6, and 1 ring of 5 carbon atoms

Many different molecules in order to:

– Increase potency and effectiveness
– Decrease classical side effects and allergenicity
Positive patch-test reactions occur less frequently with $C_{16}$-methylated or halogenated molecules.
C_{16}-methyl substitution

Previously considered as a protection against hydrolysis

Recent experimental data indicated:

- Interference with protein binding (avoidance of the formation of stable cyclic adducts with arginine)
Halogenation

Important role of stabilisation

Molecular charge difference (Wilkinson 1995, 2000)
Corticosteroid classification

Classification of CSs (according to clinical and structural characteristics):

– Coopman et al. (1989): A,B,C et D
– Matura et Goossens (2000): A,B,C,D1,D2
  (further clinical data)
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<th>TYPICAL MEMBERS</th>
<th>CROSS-REACTIONS</th>
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<tbody>
<tr>
<td><strong>A</strong></td>
<td>No substitution on the D ring except a short chain ester or a thioester on C21</td>
<td>Cortisone acetate &lt;br&gt; Hydrocortisone &lt;br&gt; Hydrocortisone acetate &lt;br&gt; Hydrocortisone 21-butyrate &lt;br&gt; Methylprednisolone acetate &lt;br&gt; Prednisolone &lt;br&gt; Prednisolone caproate &lt;br&gt; Prednisone &lt;br&gt; Tixocortol pivalate</td>
<td>D2</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>C16, C17 cis Ketal or diol structure &lt;br&gt; Possibly a side chain on C21</td>
<td>Amcinonide &lt;br&gt; Budesonide &lt;br&gt; Desonide &lt;br&gt; Triamcinolone &lt;br&gt; Triamcinolone acetonide</td>
<td></td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>C16-methyl substitution on the D ring &lt;br&gt; Halogen substitution &lt;br&gt; No side chain on C17 &lt;br&gt; Possibly a side chain on C21</td>
<td>Betamethasone &lt;br&gt; Dexamethasone &lt;br&gt; Dexamethasone acétate &lt;br&gt; Diflucortolone valerate &lt;br&gt; Flucortolone</td>
<td></td>
</tr>
<tr>
<td><strong>D1</strong></td>
<td>C16-methyl substitution &lt;br&gt; Halogen substitution &lt;br&gt; Side chain ester on C17 &lt;br&gt; Possibly a side chain on C21</td>
<td>Betamethasone dipropionate &lt;br&gt; Betamethasone 17-valérate &lt;br&gt; Clobetasol propionate &lt;br&gt; Clobetasone butyrate &lt;br&gt; Fluticasone propionate &lt;br&gt; Mometasone furoate</td>
<td></td>
</tr>
<tr>
<td><strong>D2</strong></td>
<td>No methyl substitution on C16 &lt;br&gt; No halogen substitution &lt;br&gt; Side chain ester on C17 &lt;br&gt; Possibly a side chain on C21</td>
<td>Difluprednate &lt;br&gt; Hydrocortisone aceponate &lt;br&gt; Hydrocortisone 17-butyrate &lt;br&gt; Methylprednisolone aceponate &lt;br&gt; Prednicarbate</td>
<td>A &lt;br&gt; Budesonide (S isomer)</td>
</tr>
</tbody>
</table>
Corticosteroids cross-reactivity

Sensitized patients often test positive to several CSs (85%):

– Concomitant reactions/subsequent sensitization
– Cross-reactions (also reactions to not locally available CSs)
  • Intra-group
  • Inter-group
    A and D2
    Budesonide and D2
Corticosteroid series
Molecular modelling and 3D-QSAR

Comparison between:

– molecular modelling and clustering of CSs (by electrostatic and steric fields)

– and patch-test results (with a series of 66 CSs in 315 previously sensitized subjects)
• Alignment on the common steroid skeleton.
• Optimization of the alignment by rotations of lateral side chains.
- Insertion of superposed molecules in a grid with probes and computerisation of steric/electrostatic fields

- Statistical analysis.
• All $C_{21}$ and $C_{17}$ CS esters were hydrolyzed

• Results are in accordance with clinical data

• Optimal cut: 3 clusters
Composition of the clusters:

– C-1: molecules mostly from group A and D2 without \(C_{16}\)-methyl substitution nor halogenation, and budesonide

– C-2: halogenated molecules of the acetonide group B

– C-3: halogenated molecules from group C and D1, \(C_{16}\)-methylated
- Correlation clinical data / dendrogram
- All patients positive to clusters 2, 3 also reacted to cluster 1, BUT the opposite was not the case

2 patient profiles:
- **Profile 1**: Cluster 1 (+) only
- **Profile 2**: Cluster (+) : 1 and 2
  Cluster (+) : 1 and 3
  Cluster (+) : 1, 2 and 3
2 patient subtypes

Profile 1: allergic to molecules of Group 1 only

Profile 2: possibly allergic to molecules of the 3 groups

3D-QSAR identified different areas of recognition
Respective contribution of electrostatic and steric fields

Profile 1:

– ELECTROSTATIC FIELDS or molecular charge important
– Reactions mainly to non-halogenated molecules, halogen substitution on C6 being protective
Patient profile 1 : 3D-QSAR

3D-QSAR study for profile 1 patients: electrostatic fields (blue and red) being predominant
Respective contribution of electrostatic and steric fields (2)

Profile 2:

– STERIC FIELDS or molecular structure important
– Common structural cycles (despite certain diversity)
– Possible reactions to any CS molecule
– Systematic, individualized evaluation of the sensitization/tolerance profile necessary
Patient profile 2 : 3D-QSAR

3D-QSAR study for profile 2 patients: steric fields (yellow and green) being predominant.
## Reappraisal of the classification

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<th>GROUPS</th>
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<th>MEMBERS</th>
</tr>
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</table>
| 1 (A, D2 and budesonide) | No $C_\text{16}$-methyl substitution  
No halogen substitution in most cases | Cortisone acetate  
Hydrocortisone  
Hydrocortisone acetate  
Methylprednisolone acetate  
Prednisolone  
Prednisone  
Tixocortol pivalate  
Hydrocortisone aceponate  
Hydrocortisone 17-butyrate  
Methylprednisolone aceponate  
Budesonide  
Triamcinolone |
| 2 (B) | $C_\text{16} / C_\text{17}$ Cis ketal or diol structure  
Halogen substitution except* | Amcinonide  
Desonide*  
Triamcinolone acetonide  
Halcinonide* |
| 3 (C, D1) | $C_\text{16}$-methyl substitution  
Halogen substitution | Betamethasone  
Dexamethasone  
Dexamethasone acétate  
Diflucortolone valerate  
Flucortolone  
Betamethasone dipropionate  
Betamethasone 17-valérate  
Clobetasol propionate  
Clobetasone butyrate  
Fluticasone propionate  
Mometasone furoate |
Budesonide...a particular position

R and S isomers

– R = Cross-reactions with acetonides
– S = Cross-reactions with Group 1 (A and D2)
1. Diagnostic

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Practical guidelines

Confirmation of corticosteroid allergy
- European Standard Series (tixocortol pivalate, budesonide, HC-17 butyrate)
- Personal corticosteroids used

Determination of the patient profile
- Additional patch tests with groups 2 and 3 corticosteroid molecules
Corticosteroid series

- Fluocortin butyl
- Amcinonide
- Desonide
- Alclomethasone dipropionate
- Betamethasone dipropionate

- Triamcinolone diacetate
- Triamcinolone acetonide
- Fluocortolone pivalate
- Diflorasone diacetate
- Fluocortolone caproate ou 21-hexanoate

At least one +
Patient profile 2: possibly allergic to any CS
All molecules need to be tested

All tests -
Patient profile 1: allergic to group 1 only
OK groups 2 and 3

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Take home message

Corticosteroid allergy: think about it!

Testing with the specific corticosteroid used

Allergic reactions less frequent with $C_{16}$-methylated or halogenated CS molecules (Groups 2 and 3)

2 patients subtypes

– 1: Allergic to the non-methylated and/or non-halogenated molecules
– 2: possibly allergic to the entire spectrum of CSs
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