SKIN TESTING IN DIAGNOSIS OF HYPERSENSITIVITY DRUG REACTIONS

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Associate Professor, Faculty of Medicine, Nancy, France
GENERAL CONSIDERATIONS

• Skin test is the most widely procedure in the evaluation of drug allergy
• Indicated in those reactions where specific immunological mechanisms are involved.
• Diagnose based on history in unreliable
• Lack of sufficient validated information concerning drug concentrations.
• Only validation for a limited number of drugs.
• The approach is based in the local induction of a response indicative of the mechanism that induced the reactions.
GENERAL CONSIDERATIONS

• Hypersensitivity drug reactions are associated to consumption patterns.

• Consumption patterns differ in the populations.

• Other variables may contribute also to the response

• Anamnestic response does not last for ever.
DIAGNOSTIC APPROACH

- CLINICAL HISTORY.
- SKIN TESTS.
- IN VITRO TESTS
- DRUG PROVOCATION TESTS.
TYPE OF REACTIONS

Gell & Coombs Classification

Type 1

- APC: Antigen processing and presentation
- T Lymphocyte
- IL4
- Antigen
- B Cell
- Antigen binding by IgE
- Mast cell
- Mediator Release

Type 2

- Lysis by Complement
- Opsoporation and phagocytosis
- Antibody dependent toxicity
- Macrophage
- Phagocytosis
- Lysis

Type 3

- Immune Complex
- Immunoprecipitates
- Neutrophil attraction
- Lesion

Type 4

- APC
- NK
- Cytoquines
- Tc
- Inflammatory mediators
- T Helper Lymphocyte
- Macrophage
## Type of Reactions

**Gell & Coombs Classification**

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Mechanisms</th>
<th>Clinical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (immediate)</td>
<td>IgE mediated</td>
<td>Urticaria, Angioedema, Anaphylaxis, Anaphylactic shock, Bronchial asthma, Rhinitis, conjunctivitis</td>
</tr>
<tr>
<td>Type II (cytotoxic)</td>
<td>Antibody mediated</td>
<td>Immune hemolytic anemia, Thrombocytopenia, Blood cell dyscrasias, Organ-specific reactions</td>
</tr>
<tr>
<td>Type III (immunocomplex)</td>
<td>Immunocomplex mediated</td>
<td>Serum sickness–like syndrome, Vasculitis, Organ-specific reactions</td>
</tr>
<tr>
<td>Type IV (delayed)</td>
<td>T cell mediated</td>
<td>Maculopapular exanthema, SJS, TEN, Organ-specific reactions, AGEP, DRESS/DHIS, Fixed drug eruption, Contact eczema, Delayed urticaria</td>
</tr>
</tbody>
</table>

**IMMEDIATE < 1 hour**

**NON IMMEDIATE > 1 hour**
PRACTICAL CLASSIFICATION

IMMEDIATE: <1 h
- IgE antibodies
- Urticaria
- Anaphylaxis

NON-IMMEDIATE: >1 h
- T cells
- Non immediate urticaria
- Maculopapular Exanthema
- Desquamative Exanthema
- Fixed Drug Eruption
- Acute generalized pustulosis
- DRESS
- Stevens Johnson/Lyell

Romano A, et al. Allergy 2004
IMMEDIATE ALLERGIC REACTIONS

- Symptoms must be compatible and occur within an interval of time shorter than one hour after drug intake.

  Anaphylaxis
  Urticaria/Angioedema.

- Patient selection, lack of differentiation between immediate and non immediate reactions and misclassifications.

SKIN TESTS FOR IMMEDIATE REACTIONS (IR)

Betalactams antibiotics
Macrolides
Aminoglycosides
Metrnonidazol
Vancomycin
Clindamycin
Trimetropin/Sulfamehoxxazol
Neuromuscular Blocking agents
Local anesthetics
Heparins, Heparinoids, Anticoagulants
Platinum salts and other antineoplastics
Contras media
NSAIDs
Opiods, Fentanyl
Biological agents
Vaccines
Corticoids
Others
Patients with clinical symptoms compatible with NSAIDs hypersensitivity

41.7±15.8 (14–80) years

Cross Intolerance 503, 76%

Selective responders 156; 24%

Doña I. Clin Exp Allergy 2010
DRUGS FREQUENTLY INVOLVED

Intradermal test

PPL, MDM, AMOXICILLIN 1/10 and 1/1 dilution
Prick test

PPL, MDM, AMOXICILLIN 1/10 and 1/1 dilution
EPIDEMIOLOGY

- BL are the most frequent elicitors of drug hypersensitivity reactions.

- Benzylpenicillin was the first reported BL involved, followed over the years by different penicillins and cephalosporins, with amoxicillin now being the drug most frequently inducing reactions.

- The prevalence and incidence of allergic reactions to BLs in the general population are not well known.

- Data vary depending on the study: over-reporting when are classified by history and underreporting of mild and severe reactions.

- Studies performed in a large series of patients with cutaneous symptoms showed that only 19% were finally diagnosed as being allergic to BLs.
**Table 2. Characteristics of Patients with Positive Drug Provocation Test Results**

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Patients, n</th>
<th>Positive Drug Provocation Test Results, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>945</td>
<td>15.4</td>
</tr>
<tr>
<td>Males</td>
<td>427</td>
<td>22.2</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤18 y</td>
<td>144</td>
<td>15.9</td>
</tr>
<tr>
<td>18–65 y</td>
<td>986</td>
<td>17.7</td>
</tr>
<tr>
<td>≥65 y</td>
<td>242</td>
<td>17.8</td>
</tr>
<tr>
<td><strong>Drug class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-lactam</td>
<td>416</td>
<td>8.4</td>
</tr>
<tr>
<td>Aspirin</td>
<td>199</td>
<td>47.2</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>161</td>
<td>27.3</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>118</td>
<td>17.0</td>
</tr>
<tr>
<td>Macrolides</td>
<td>102</td>
<td>13.7</td>
</tr>
<tr>
<td>Quinolones</td>
<td>33</td>
<td>27.3</td>
</tr>
<tr>
<td>Other†</td>
<td>343</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylactic shock</td>
<td>64</td>
<td>32.8</td>
</tr>
<tr>
<td>Anaphylaxis without shock</td>
<td>57</td>
<td>29.8</td>
</tr>
<tr>
<td>Laryngeal edema</td>
<td>90</td>
<td>27.8</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>94</td>
<td>20.2</td>
</tr>
<tr>
<td>Urticaria</td>
<td>718</td>
<td>17.8</td>
</tr>
<tr>
<td>Maculopapular eruption</td>
<td>300</td>
<td>10.3</td>
</tr>
<tr>
<td>Other‡</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td><strong>Chronology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 h</td>
<td>448</td>
<td>24.8</td>
</tr>
<tr>
<td>1–8 h</td>
<td>184</td>
<td>24.5</td>
</tr>
<tr>
<td>8–12 h</td>
<td>556</td>
<td>12.2</td>
</tr>
<tr>
<td>12–24 h</td>
<td>184</td>
<td>9.2</td>
</tr>
</tbody>
</table>
IMMEDIATE REACTIONS

- Antigen Presenting Cells
- Hapten-Protein
- T Lymphocyte
- B Lymphocyte
- B Mast-Cells
- BAT
- SKIN TESTS
- Hypersensitivity reactions
- IMMUNOASSAYS

Cell activation and mediator release.
BETALACTAM IMMUNOCHEMISTRY

A

B

PENICILLIN IMMUNOCHEMISTRY

Benzylpenicillin + Protein → Bencilpenamaldil

Benzylpenicilloyl (MAJOR DETERMINANT) + Bencilpenaldil (MINOR DETERMINANTS)
EVOLUTION OF RESPONSE

Benzylpenicilloil
Benzylpenicillin
Benzylpenicilloic acid
Bencilpenilloic

NH₂
OH
N
S
COOH
N
H
H
O
H
CH₃
CH₃
CH₃
COOH

PPL
MDM
AX
AMP

Blanca M 1990
Torres MJ 2001
Blanca M 2007
## SKIN TESTS

<table>
<thead>
<tr>
<th>HAPTEN</th>
<th>DOSE</th>
<th>UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPL</td>
<td>$5 \times 10^{-5}$</td>
<td>mmol/L</td>
</tr>
<tr>
<td>MDM</td>
<td>$2 \times 10^{-2}$</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>20</td>
<td>mg/ml</td>
</tr>
<tr>
<td>BP</td>
<td>10,000</td>
<td>IU/ml</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>2</td>
<td>mg/ml</td>
</tr>
</tbody>
</table>

Rodriguez-Bada JL et al, Allergy 2006
AMOXICILLIN DETERMINANTS

AMOXICILLIN

Autoaminolysis

Hydrolysis

DIKETOPIPERACINE

AMOXICILIOIC ACID

Torres MJ. Allergy 2009
Penicillin Allergy: Value of Including Amoxicillin as a Determinant in Penicillin Skin Testing

Erina Lin  Andrew Saxon  Marc Riedl

The Hart and Louis Laboratory, Division of Clinical Immunology and Allergy, Department of Medicine, UCLA David Geffen School of Medicine, Los Angeles, Calif., USA

Table 1. Positive results to the various penicillin reagents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Males (n = 89; 37%)</th>
<th>Females (n = 154; 63%)</th>
<th>Total (n = 243; 23%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicilloyl-polylysine</td>
<td>56 (62.9)</td>
<td>101 (65.6)</td>
<td>157 (64.6)</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>37 (41.6)</td>
<td>74 (48.0)</td>
<td>111 (45.7)</td>
</tr>
<tr>
<td>Penicilloate</td>
<td>32 (36.0)</td>
<td>58 (37.7)</td>
<td>90 (37)</td>
</tr>
<tr>
<td>Penilloate</td>
<td>31 (34.8)</td>
<td>53 (34.4)</td>
<td>84 (34.6)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>28 (31.5)</td>
<td>47 (30.5)</td>
<td>75 (30.9)</td>
</tr>
<tr>
<td>Penicilloyl-polylysine only</td>
<td>16 (18.0)</td>
<td>29 (18.8)</td>
<td>45 (18.5)</td>
</tr>
<tr>
<td>Penicillin G only</td>
<td>8 (9.0)</td>
<td>8 (5.2)</td>
<td>16 (6.6)</td>
</tr>
<tr>
<td>Penicilloate only</td>
<td>3 (3.4)</td>
<td>4 (2.6)</td>
<td>7 (2.9)</td>
</tr>
<tr>
<td>Penilloate only</td>
<td>5 (5.6)</td>
<td>11 (7.4)</td>
<td>16 (6.6)</td>
</tr>
<tr>
<td>Combination 1</td>
<td>21 (23.6)</td>
<td>34 (22.1)</td>
<td>55 (22.6)</td>
</tr>
<tr>
<td>Combination 2</td>
<td>13 (14.6)</td>
<td>26 (16.9)</td>
<td>39 (16)</td>
</tr>
<tr>
<td>Amoxicillin only</td>
<td>5 (5.6)</td>
<td>9 (5.8)</td>
<td>14 (5.8)</td>
</tr>
</tbody>
</table>

Results are numbers of patients (percentages in parentheses). Combination 1 = combination of the minor determinants penicillin G, penicilloate and penilloate. Combination 2 = combination of the minor determinants penicilloate and penilloate.

19% were only ST positive to amoxicillin
SENSITIVITY OF THE DIAGNOSTIC METHODS

N= 257
Confirmed BL allergy

DPT 31%
SKIN TEST 69%

Bousquet PJ. Clin Exp Allergy 2008

N= 290
Confirmed BL allergy

IN VITRO

DPT 13%
SKIN TEST 70%

Torres MJ et al, Allergy 2001

DPT is still needed for confirming the diagnosis and has to be performed in patients with suspected antibiotic allergy.
## BETALACTAMS INVOLVED

### Table 2
**Classification of penicillins and cephalosporins**

<table>
<thead>
<tr>
<th>Group</th>
<th>Compounds</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penicillins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural</td>
<td>Penicillin G, penicillin V</td>
<td></td>
</tr>
<tr>
<td>Aminopenicillins</td>
<td>AX, ampicillin, bacampicillin</td>
<td></td>
</tr>
<tr>
<td>Penicillinase-Resistant</td>
<td>Methicillin, oxacillin, cloxacillin, nafcillin, dicloxacillin</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>Carboxypenicillins</td>
<td>Carbenicillin, ticarcillin</td>
<td></td>
</tr>
<tr>
<td>Acylaminopenicillins</td>
<td>Azlocillin, mezlocillin, piperacillin</td>
<td></td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Generation</td>
<td>Cefadroxil, cephalexin, cephalotin, cepapirin, cefazolin, cefprozil, cefradine</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>Second Generation</td>
<td>Cefaclor, cefamandole, cefmetazole, cefminox, cefonicid, ceforanide, cefotetan, cefotiam, cefoxitin, cefuroxime, loracarbef</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>Third Generation</td>
<td>Cefdinir, cefetamet, cefixime, cefodizime, cefoperazone, cefotaxime, cefpodoxime, ceftizoxime, cefpiramide, cefsulodin, ceftazidime, ceftibuten, ceftriaxone</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>Fourth Generation</td>
<td>Cefepime, cefpirome</td>
<td></td>
</tr>
</tbody>
</table>

CLAVULANIC ACID SPECIFICITIES

Amoxicillin

Clavulanic

AX-CLV CONSUMPTION IN 2008

- HOSPITAL: 6,000,000 units
- TOTAL: 20,000,000 units/year

Torres MJ. JACI 2010
MEAN AGE IN THE DIFFERENT GROUPS

Skin testing in IR

Group Penicillins

Group Amoxicillin

Group Clavulanic

P<0,025

P<0,005

P<0,025

P<0,005

Torres MJ. JACI 2010
CHEMICAL STRUCTURE

PENICILLINS

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Benzylpenicillin" /></td>
<td>Benzylpenicillin</td>
</tr>
<tr>
<td><img src="image" alt="Amoxicillin" /></td>
<td>Amoxicillin</td>
</tr>
<tr>
<td><img src="image" alt="Ampicillin" /></td>
<td>Ampicillin</td>
</tr>
</tbody>
</table>

CEPHALOSPORINS

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Cefaclor" /></td>
<td>Cefaclor</td>
</tr>
<tr>
<td><img src="image" alt="Cefuroxime" /></td>
<td>Cefuroxime</td>
</tr>
<tr>
<td><img src="image" alt="Ceftazidime" /></td>
<td>Ceftazidime</td>
</tr>
<tr>
<td><img src="image" alt="Ceftriaxone" /></td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td><img src="image" alt="Cefotaxime" /></td>
<td>Cefotaxime</td>
</tr>
<tr>
<td><img src="image" alt="Cefonicid" /></td>
<td>Cefonicid</td>
</tr>
<tr>
<td><img src="image" alt="Cefadroxil" /></td>
<td>Cefadroxil</td>
</tr>
</tbody>
</table>
BACKGROUND

positive to penicillins

negative to penicillins

Culprit cephalosporin
63.2%

Different cephalosporins
36.8%

Shared the same side chain at R₁ position

Cefuroxime

Cefotaxime

Ceftriaxone

Antúnez C. JACI 2006.
Most of the studies of immediate allergic reactions to cephalosporins have been carried out by selecting more or less well defined groups who were originally allergic to penicillin and evaluating if they could safely take cephalosporins.

As consumption of cephalosporins rises, patients are evaluated after an immediate allergic reaction to cephalosporins, with the number of selective cases increasing.

- Crossreactive Penicillin 18%
- Cephalosporin selective 82%

Romano A et al. JACI 2000
DIAGNOSTIC ALGORYTHM

CLINICAL HISTORY AND BLOOD SAMPLE

Prick PPL/MDM

ID PPL/MDM

Test In vitro

AC con BP

1 week

Prick Drug

ID Drug

DPT with the drug

ALLERGIC
- Non selective reactions
- Selective reactions

Decrease of systemic reactions

Non ALLERGIC

SKIN TEST, RAST AND BAT SENSITIVITY OVER TIME

% survival of skin test positive

Nonselective reactions
Selective reactions

Cumulative survival

P = 0.0167
Log Rank = 5.73

Blanca M, et al, JACI 1999

SKIN TEST TO METAMIZOL
Two cases with anaphylactic reactions

PRICK

<table>
<thead>
<tr>
<th>PRICK:</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg/ml</td>
</tr>
<tr>
<td>40 mg/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ID:</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mg/ml</td>
</tr>
<tr>
<td>0.4 mg/ml</td>
</tr>
</tbody>
</table>
SKIN TEST RESULTS CONTRAST MEDIA
Immediate reactions

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>163 (97.1%)</td>
</tr>
<tr>
<td>Positive</td>
<td>5 (2.9%)</td>
</tr>
</tbody>
</table>

Iohexol

Iodixanol
Most of the reactions were mild (62.5%), being all skin test negative. 72 (68.6%) patients were administered RCM with pre-medication with good tolerance. Therefore, an IgE mechanism could not be demonstrated.

Eight cases (4.8%) were finally confirmed as allergic (5 by skin testing and 3 by DPT). All were moderate or severe reactions (urticaria and anaphylaxis). This means that the diagnosis was confirmed in 12.78% of patients with moderate and severe reactions, results similar and those previously reported.

Moreover, two cases with skin test positive were DPT positive to alternatives with skin test negative.

BAT was positive in 5 (62.5%) cases with skin test or DPT positive, with a good correlation between the RCM inducing in vivo positive tests and in vitro tests.
ROLE OF SKIN TESTING IN EVALUATING CROSS REACTIVITY 
PENICILLIN-CEPHALOSPORINS

Same side chain

- 24 patients with ST (+) to AX and good tolerance to BP
- 25% were ST (+) to CXO
- One patient (4%) were ST (-) and DPT (+) to CXO.
SKIN TESTS FOR NON IMMEDIATE REACTIONS (NIR)

All soluble drugs considered in IR (ID)
Non soluble BLs /No parenteral available (PT)
Oral and topical formulations (PT)
Anticonvulsivants (PT)
NSAIDs (eg propifenazon) (PT)
Corticoids (PT)
Hormones (PT)
Antivirals (PT)
Antihypertensive (PT)
Others
DRUG PATCH TESTING
Non-immediate reactions

Performed in the upper back with chamber or tapes

Usually reading at 48 hours (from 24 h up to 7 days)

Most marketing drugs can be used (≤30% w/w) in petrolatum

Saline and alcohol can be used as diluent

Pure substances whenever possible

Consider suboptimal concentrations (0.1 to 1%) in severe reactions

Barbaud A. Contact Dermatitis 2001;45:321
INTRADERMAL DRUG TESTING
Non-immediate reactions

Dilutions prepared under sterile conditions two hours before testing

Sterile saline with the drug already diluted in vehicle included

Usually in external surface of arm

Sequential dilutions may be necessary (10^{-4} to 10^{-1} mgs)

Non irritant concentrations must be established in negative controls

Usually 24-48 hours, longer or higher intervals may be needed

Controversies on contraindications in severe reactions

Barbaud A. Contact Dermatitis 2001;45:321
PATCH TESTING

PPL, MDM AMOXICILLIN 1/10 and 1/1 dilution
MPE INDUCED BY METAMIZOL

PATCH TEST + METAMIZOL
NON IMMEDIATE ALLERGIC REACTIONS
T cell dependent responses

- Heterogeneity of the clinical manifestations.
- Similar to infectious or autoimmune diseases.
- Facilitation by a concomitant viral infection (HIV, CMV, HHV 6, EBV).
- A high proportion of subjects with exanthematic reactions to BL show good tolerance.
- Skin rash in children is only rarely reproducible (6.8%) by DPT (Caubert JC. JACI 2011)
NON IMMEDIATE REACTIONS

SKIN TESTS

Drug

DC

Keratinocyte

NK

Mature DC

Macrophage

IL-12

LTT

CD4$^+$ T Lymphocyte

Lymphoid node

SKIN TESTING
Intradermal versus patch testing

- ID test/patch testing sensitivity: 60-100%.
- ID test sensitivity is higher.
- Sensitivity is maintained over time.
- Higher in more severe reactions???

Cross-reactivity between penicillins and cephalosporins seems to be very rare for T-cell reactions.

This can be verified by cutaneous testing.

SKIN TESTS

History of NIR
N=146

DPT

Non Allergic
N=124

Allergic
N=22

IDT/PT

Positive
N=2

SKIN TEST SENSITIVITY IS LOWER THAN PREVIOUSLY THOUGHT.

N=20 children with NIR

- Maculopapular exanthema and urticarial-like exanthema.
- 1 skin test positive and 19 DPT positive.
Rate of Adverse Reactions to Penicillins and/or Cephalosporins are Low in Children with a Negative Penicillin Skin Test

Stephanie J Fox MD, Miguel P Park, MD
Division of Allergic Diseases, Mayo Clinic, Rochester, MN

Distribution of results in children with positive penicillin skin tests.
*Note that children can test positive to more than one reagent.

- 66 children positive
- 41 positive to major determinant
- 40 positive to minor determinant
- 24 positive to amoxicillin

AAAIAI. New Orleans 2010
Original article

Nonimmediate reactions to systemic corticosteroids suggest an immunological mechanism

Background: Administration of corticosteroids (CS) by different routes may cause varying types of allergic reactions, thereby hampering their further use in affected patients. In order to verify an immunological involvement we evaluated a group of patients with symptoms compatible with nonimmediate allergic reactions to CS.

Methods: Studies included patch and intradermal tests, immunohistochemical studies and controlled administration to reproduce the response. The cytokines interleukin (IL)-4, interferon (IFN)-γ and tumor necrosis factor (TNF)-α were quantified in peripheral blood during the response.

Intradermal

Patch

A. Padial¹, S. Posadas¹, J. Alvarez², M.-J. Torres³, J. A. Alvarez¹, C. Mayorga³, M. Blanca¹

¹Servicio de Alergología, ²Departamento de Anatomía Patológica, Hospital Universitario La Paz, Madrid, ³Servicio de Alergología, Hospital Universitario Carlos Haya, Málaga, Spain
Non-Immediate reactions to contrast media
24 hours reading

- Iomeprol
- Iodixanol
- Ioxaglate
- Iohexol
MPE INDUCED BY METAMIZOL

PATCH TEST + METAMIZOL
<table>
<thead>
<tr>
<th>Type of Adverse Effects to Biologicals</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytokines</strong></td>
<td>IFN-a, IFN-b, IL-2, etc</td>
</tr>
</tbody>
</table>
| **Antibodies** | To soluble proteins like cytokines: anti-TNF-a (infliximab or adalimumab), anti-IL-2 (daclizumab)  
To cell surface molecules: anti-CD20 (rituximab); anti-IL-2 receptor (basiliximab), anti-LFA-1 (efalizumab)  
To IgE (omalizumab)  
To tumour antigens (e.g. EGFR, cetuximab, anti-HER2, trastuzumab) |
| **Fusion proteins** | TNF-aRII (etanercept), a soluble TNF-a receptor  
CTLA4-Ig (abatacept) blocking CD28–CD80/CD86 interaction  
IL-1 receptor antagonist (anakinra)* |
| **Immune Modulators** | Copaxone, Corticosteroids. |
**BIOLOGICALS: DRUG TESTING AND DESENSITISATION**

![Image of skin reactions to various substances](image)

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Pork-cat syndrome (control subject)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef</td>
<td>3.43</td>
<td>20</td>
<td>6.11</td>
</tr>
<tr>
<td>BSA</td>
<td>ND</td>
<td>ND</td>
<td>10.8</td>
</tr>
<tr>
<td>Pork</td>
<td>2.38</td>
<td>13</td>
<td>6.48</td>
</tr>
<tr>
<td>Pork serum albumin</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
<td>9.41</td>
</tr>
<tr>
<td>Rabbit</td>
<td>0.62</td>
<td>1.12</td>
<td>ND</td>
</tr>
<tr>
<td>Cat epithelia</td>
<td>2.28</td>
<td>20.3</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Cat albumin</td>
<td>&lt;0.10</td>
<td>0.14</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Fel d 1</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
<td>3.01</td>
</tr>
<tr>
<td>α-Gal</td>
<td>4.82</td>
<td>0.28</td>
<td>&lt;0.10</td>
</tr>
</tbody>
</table>

**Specific IgE levels**

Jacquenet S. JACI 2009
CONCLUSIONS

Skin testing is the most validates and generalised aproachc for evaluating allergic drug reactions (IgE or T cell dependents).

Both drugs and bilological agents can be used

Non aplicable in other mechanisms (E.g. Cross-Intolerant NSAIDs hypersesnsitivity.

Sensitivity depend on the mechanisms involved and drug used.

Specificity depend on the intrinsic properties of the drugs and of the methods used.

Phsicochemical properties of the drug are relevant for skin test performance

Sensivity can be lost over time,