Respiratory type of Hypersensitivity to NSAIDs

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Adverse Drug Reactions

**Type A** (70-90%)
- Common and predictable
- In normal individuals
- Dose-dependant
- **NSAIDs:**
  - Gastrointestinal
  - Renal

**Type B** (10-30%)
- Unpredictable
- In susceptible individuals

Drug hypersensitivity
- Allergic
- Non-allergic
Drug hypersensitivity at the University Hospital Allergy Clinic in Łódź

In 2005 and 2006

- 4511 new patients were referred to the Clinic
- 313 patients (6.7%) reported drug hypersensitivity

Number of patients

- NSAIDS: 169
- ANTIBIOTICS: 135
- OTHER: 9

Makowska J et al. 2008
## Classification of Hypersensitivity reactions to NSAIDs

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Type of reaction</th>
<th>Underlying disease</th>
<th>Putative mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinitis/asthma</td>
<td>Cross-reactive</td>
<td>Asthma/rhinosinusitis/nasal polyps</td>
<td>Inhibition of COX-1</td>
</tr>
<tr>
<td>Urticaria/angioedema</td>
<td>Cross-reactive</td>
<td>Chronic urticaria</td>
<td>Inhibition of COX-1</td>
</tr>
<tr>
<td>Urticaria/angioedema</td>
<td>Multiple NSAIDs-induced</td>
<td>No underlying chronic disease.</td>
<td>Unknown. Presumably related to Cox-1 inhibition</td>
</tr>
<tr>
<td>Urticaria/angioedema/ anaphylaxis</td>
<td>Single drug induced</td>
<td>Atopy, Food allergy Drug allergy</td>
<td>IgE-mediated</td>
</tr>
<tr>
<td>Blended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DELAYED</td>
<td>various</td>
<td>None or various</td>
<td>DTH, various</td>
</tr>
</tbody>
</table>

D.D.Stevenson, A. Szczeklik. M. Sanchez-Borges 2000
Acute hypersensitivity reactions to ASA and other NSAIDs

**Respiratory**

**Cutaneous**

Anaphylaxis and/or cutaneous cross-reacting

Single drug reactors

Cross-reacting or multiple drug
Respiratory type of hypersensitivity to NSAIDs

ASA-induced symptoms

Clinical phenotype

CRS with nasal polyps

Severe asthma

Aspirin Exacerbated Respiratory Disease (AERD)
NSAIDs Exacerbated Respiratory Disease (NERD)
Severity of CRS in ASA-tolerant and ASA-sensitive patients

Recurrence of nasal polyps after polypectomy (follow-up period of 4 years)

- **Patients with AERD** had history of 10 times as many previous FESS procedures as had the patients without aspirin sensitivty
- **ASA triad mean:** 5.2
- **ASA (-) mean:** 0.53; (p < 0.001)

CT staging of chronic rhinosinusitis in ASA-sensitive and ASA-tolerant patients

Kowalski ML et al. WAJ 2003

Jantti-Alanko S. et al. Rhinology 1989,8.59

AERD - a severe asthma phenotype

- Higher medication requirements, including dependence on oral GCS (Szczeklik A. et al. 2000)
- Irreversible airway obstruction
- More likely to have been intubated and to have a steroid burst in the previous three months (Mascia K et al. 2005)
- Frequent exacerbations (Koga T. Et al. 2006)
- Association with near fatal asthma (Plaza W. et al. 2002)

Risk factors for severe asthma

- Odds Ratio (OR) = 2.6
- BMI
- AIA
- Wheezing in childhood

ML Kowalski et al. Allergy 2010, in press
The mechanism of sensitivity to NSAIDs in patients with AERD

- **Mechanism – non immunological**
  - Cross-reacting drugs have diverse chemical structure
  - No specific immunoglobulins
  - No specific T-cells

- **Mechanism related to pharmacological activity of NSAIDs**
  - Only Cox inhibitors cross-react with ASA
  - COX-1 >>> COX-2 inhibitors

- **Biochemical abnormalities**
  - Several – related to AA metabolism e.g. decreased PGE2 generation, elevated urinary LTE4
  - Identified only in some patients
Patomechanisms of Aspirin Exacerbated Respiratory Disease

I. The acute reaction precipitated by ASA and NSAIDs

- ASA / NSAID’s
- COX-1
- Mast cell
- Leukotrienes
  - Tryptase
  - Histamine
  - ECP
  - 15-HETE
- Bronchial
  - Nasal
  - Occular symptoms

II. Chronic symptoms and underlying airway inflammation

?
### Cross-sensitivity between ASA and NSAID’s and prostaglandin inhibition

A. Szczeklik 1975/modified

<table>
<thead>
<tr>
<th>Generic name</th>
<th>PG’s inhibition</th>
<th>Cross-sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Strong</td>
<td>High - 50 - 90%</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Strong</td>
<td>High - 50 - 90%</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Strong</td>
<td>High - 50 - 90%</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Strong</td>
<td>High - 50 - 90%</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Strong</td>
<td>High - 50 - 90%</td>
</tr>
<tr>
<td>Phenylbutazon</td>
<td>Weak</td>
<td>Low &lt; 5%</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Weak</td>
<td>Low &lt; 5%</td>
</tr>
<tr>
<td>Na Salicylate</td>
<td>No</td>
<td>none or rare cases reported</td>
</tr>
</tbody>
</table>
Arachidonic acid

$\text{PGG}_2$

$\text{PGH}_2$

$\text{PGE}_2$

$\text{COX}-1$

$\text{COX}-2$

$\text{ASA}$

$\text{PLA}$

$\text{5-LOX}$

$\text{LTA}_4$

$\text{LTC}_4$

$\text{LTD}_4$

$\text{LTE}_4$

Cell membrane phospholipids

Asthma Rhinorrhea

Eosinophils

Mast cell

$\text{EP} - \text{R}$

$\text{EP} - \text{R}$
Patomechanisms of Aspirin Exacerbated Respiratory Disease

I. Acute symptoms precipitated by ASA and NSAIDs

ASA / NSAID’s → COX → EOS → Leukotrienes Tryptase Histamine ECP 15-HETE → Bronchial Nasal Occular symptoms

II. Chronic symptoms and underlying airway inflammation

Unrelated to intake of ASA or other NSAIDs !!!
Pathogenesis of eosinophilic inflammation in patients with AERD

- **AA abnormalities**
- **Allergy**
- **Infections**

Intractable inflammation in upper and lower airway mucosa poorly responding to steroids

- Infiltration with Eosinophils and Mast cells
- Increased mobilisation of Eos progenitors / decreased apoptosis
- Mixed Th2/Th1 IL-5/IL13
- Overproduction of CysLTs /PGD2 and LXA4 deficiency

Allergy

Infections

AA abnormalities
**Cell membrane phospholipids**

- PLA-2

**Arachidonic acid**

- 12-HETE

**12-LO**

- 5-LO

- 15-LO

**15-HETE**

- Lipoxins

<table>
<thead>
<tr>
<th><strong>Lipoxins</strong></th>
<th><strong>PGG_2</strong></th>
<th><strong>PGH_2</strong></th>
<th><strong>PGF_2</strong></th>
<th><strong>PGD_2</strong></th>
<th><strong>LTA_4</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PGE_2</strong></td>
<td><strong>PGL_2</strong></td>
<td><strong>TXB_2</strong></td>
<td></td>
<td></td>
<td><strong>LTC_4s</strong></td>
</tr>
<tr>
<td><strong>LTC_4</strong></td>
<td><strong>LTD_4</strong></td>
<td><strong>LTE_4</strong></td>
<td><strong>LTA_4</strong></td>
<td><strong>LTB_4</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Possible Effects**

- Specific release of 15-HETE upon ASA challenge
- Abnormal lipoxins generation
- Decreased production of PGE2
- Downregulation of Cyclooxygenase-2
- Increased generation of cysLTs (urine, BAL, EAC)
- Overexpression of LT receptors
Diagnosis of respiratory type of hypersensitivity to NSAIDs

- **History**
- **Aspirin challenge**
  - Oral
  - Inhaled
  - Intranasal
- **In vitro testing**
  - Cellular activation tests
    - BAT
    - ASPITest (15-HETE)
  - Urinary LTE4
- **Genetic testing**

**Aspirin-Sensitive Patients Identification Test (ASPITest)**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>PPV</th>
<th>Specificity</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPITest</td>
<td>82%</td>
<td>79%</td>
<td>83%</td>
<td>86%</td>
</tr>
</tbody>
</table>

M.L.Kowalski et al. Allergy 2005, 60, 1139-45
Arachidonic acid

- COX-1
  - PGE, PGl2, TXB2
  - Cytoprotection, Regulation

- COX-2
  - Prostaglandins
  - Inflammation

- Aspirin

- Celecoxib
Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) – classification, diagnosis and management: review of the EAACI/ENDA# and GA2LEN/HANNA*
Tolerance of NSAIDs by sensitive patients: ENDA/GA2LEN classification

- **Group A.** NSAIDs cross-reacting in majority of hypersensitive patients (60-100%)

- **Group B.** NSAIDs cross-reacting in minority of hypersensitive patients (2-10%)

- **Group C.** NSAIDs well tolerated by all hypersensitive patients*

M.L. Kowalski et al. Allergy 2011
Management of AERD

Avoidance of NSAIDs
- Recommendations for selective COX-2 inhibitors

Pharmacologic treatment
- Intranasal/inhaled/oral glucocorticosteroids
- Leukotriene antagonists

Sinus surgery/polypectomy
- Less effective in ASA-sensitive

Aspirin desensitization
- Clinical effects: risks / benefits
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