Reactions to ASA/NSAIDS/and Additives – How Do We Evaluate?

PAAA

Hershey, PA 6/21/13

R. Simon, MD
Head, Division Allergy Asthma and Immunology
Scripps Clinic
Adj. Member, Dept. Mol. & Exp. Med.
The Scripps Research Institute
La Jolla, CA
Member, NIAID Expert Food Panel
Disclosures

- None for this talk
Objectives

• Following completion of this presentation, attendees should be able to:
  • 1. Diagnose and treat patients with a history of reactions to ASA/NSAID’s
  • 2. Recognize and evaluate patients with a history of reactions to food & drug chemical additives
  • 3. Recognize and diagnose patients with a history of anaphylaxis to natural food additives
<table>
<thead>
<tr>
<th>Reaction Type</th>
<th>Underlying Disease</th>
<th>Cross Reactions</th>
<th>Arachidonic Acid Dysfunction</th>
<th>Probable IgE</th>
<th>Possible Cellular Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross Reacting Respiratory</td>
<td>Rhinitis, polyps sinusitis, asthma</td>
<td>ASA/NSAID</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cross Reacting Urticaria</td>
<td>Chronic urticaria</td>
<td>ASA/NSAID</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Urticaria/ Anaphylaxis</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>NSAID Induced Aseptic Meningitis</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>NSAID Induced Hypersensitivity Pneumonitis</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Classification of Cutaneous Reactions to Cox-1 Inhibitors - SIMPLIFIED

- NSAID-Induced urticaria/angioedema
  - Any Cox-1 inh;
    - normals
    - CIUA
- Single drug-induced urticaria/angioedema
  - Single drug-induced anaphylaxis
- Other/ “blended” reactions
Approach to Cutaneous Reactors to Cox-1 Inhibitors

- **NSAID-Induced urticaria/angioedema**
  - Any Cox-1 inh;
  - Normals: can be desensitized
  - CIUA: cannot be desensitized

- **Single drug-induced urticaria/angioedema/anaphylaxis**
  - ASA OK
  - Give a different NSAID
  - If unknown: ASA challenge

- **Other/ “blended” reactions**

- **Celecoxib ( & other highly selective Cox2 inh) always OK**
# Approach to Cutaneous Reactors to Cox-1 Inhibitors

- Provocation tests with offending NSAID
  - 159 patients to start
  - Only 17 patients (10.69%) had + reaction to challenge
  - Only 8 had – challenge to another Cox1 inh (0.05%)

  **Way to few to conclude it is safe to challenge with historically + Cox1 inh**

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Approach to Cutaneous Reactors to Cox-1 Inhibitors

• Approach in patients with cardiac emergency

• Prevention of reactions in outpatient setting
  — Desloratidine/montelukast pre-treatment
  — 1/65 reacted
Specific Food Additives

- Preservatives
- Stabilizers
- Conditioners
- Thickening agents
- Sweetening agents
- Food coloring
- Flavoring agents
- Antioxidants
- Miscellaneous food additives
## Contents of Premarin Tablets

*(Brown, 0.625mg)*

- Methylcellulose 15 CPS
- Talc Titurate
- Lactose
- Magnesium stearate
- Polyethylene glycol 20,000
- Glycercyl monooleate
- Shellac
- Calcium sulfate
- Titanium dioxide
- Stearic acid
- Edible black ink (Food grade)
- Carnuba wax
- Corn starch
- Sucrose
- Gum acacia
- Talc
- Sodium benzoate
- Gelatin
- Tween 60
- Propyl paraben
- FD&C Yellow #5
- Calcium carbonate
- Tricalcium phosphate
- Soda floc
- Sodium acetate
- Sodium chloride
- Neutral steroids
- Estrogens
Additives Most Commonly Associated With Adverse Reactions

- FD&C Dyes
  - Tartrazine (FD&C yellow #5)
- Parabens
  - Parahydroxy benzoic acid
    - Methyl
    - Ethyl Butyl
    - Parabens
  - Sodium benzoate
- Butylated hydroxyanisole (BHA)
- Butylated hydroxytoluene (BHT)
- Nitrates/Nitrites
- Monosodium glutamate (MSG)
- Sulfites
  - Sulfur Dioxide
    - Sodium
    - Potassium
    - Sulfite
    - Bisulfite
    - Metabisulfite
- Aspartame (Nutrasweet)
Tartrazine (FD & C Yellow No. 5)
Tartrazine and Initial Reports of Adverse Reaction

- **Purpose:** Coloring Agent
- **Dosage:** 0.1–25mg
- **Reactions Reported:** Asthma Urticaria

• Three patients with history of reaction to meds containing tartrazine:
  - **Patient #1:** In midst of generalized cutaneous eruption not tartrazine related; no challenge
  - **Patient #2:** Challenged; open sublingual; reacted
  - **Patient #3:** Challenged; open, sublingual; mild complaints localized to mouth

1. Lockey S. Ann Allergy 1959:17;719-725.
Reactions to Additives

- **High Risk Groups**
  - Chronic Urticaria
  - Asthma
Additive Challenges in CIUA
Recent Example

- 838 consecutive CIUA patients
- Results:
  - DBPC mixed additive (#6): 116 + (13.8%)
  - Only 24 (or 31) were + when repeated as single additives (~ 3%)

Additive Challenges in CIUA/AD
Most Recent Example

• 54 Korean patients; CIUA or AD
• Challenge: mixture of 6 additives
• Results:
  – 44 (81.5%) no reactions (additives or placebos)
  – 5 (9.3%) reacted only to additive
  – 2 (3.3%) reacted to both additives and placebo
  – 3 (5.5%) reacted only to placebo

Prevalence of Sensitivity to Food/Drug Additives in Patients with Chronic Idiopathic Urticaria and Angioedema (CIUA)
CIUA

Definition

- Subjects (n = 110) with hives (with or without swelling) persisting for more than 6 weeks without cause
- Excluded causes
  - Cutaneous Vasculitis
    - Hx, exam
    - Esr, complement activation
    - Biopsy (n = 40)
  - Autoimmune
    - Various serum autoantibodies (n = 35)
  - Physical Urticaria
    - Hx
    - Challenges (MCH, cold vibration, pressure) (n = 40)
Demographic Data

- 100 subjects, 64 females, 36 male
- Ages: 14-67
- Average duration of hives (mos.)
  - Mean: 9
  - Range: 3-52
- Hx adverse reactions food/drug additives (n = 43)
  - Sulfite (n = 5)
  - FD&C yellow #5 (n = 14)
  - Sulfite + FD&C yellow #5 (n = 8)
  - MSG (n = 10)
  - FD&C red #40 (n = 2)
  - FD&C blue #1 (n = 1)
  - "Preservatives/chemicals" (n = 15)
<table>
<thead>
<tr>
<th>Additives Tested/Dose (mg)</th>
</tr>
</thead>
</table>
| FD&C yellow #5                   | 50  
| FD&C yellow #6                   | 50  
| K+ metabisulfite                 | 100 
| MSG                              | 2500|
| Aspartame                        | 150 |
| Sodium benzoate                  | 100 |
| Methyl paraben                   | 100 |
| BHT                              | 250 |
| BHA                              | 250 |
| Sodium nitrate                   | 50  |
| Sodium nitrite                   | 50  |
Results

Positive Challenges

- Single blind placebo controlled: N = 2
- Double blind placebo controlled: N = 0
Conclusions

• With 99% confidence we conclude that sensitivity to any of the 11 food drug additives in patients with CIUA is ≤ 1%

• Food/drug additives appear to be a rare cause/exacerbant of CIUA

• Therefore, avoidance is not recommended
Additives and Asthma
Asthma and Sensitivity to Tartrazine

  - Simple statement in monograph: No data presented
  - One patient
  - Double-blind placebo controlled challenges, symptoms, no PFT’s
  - 80 asthmatics (1/2 ASA sensitive)
  - Open solution challenge reaction + “Rhinorrhea and Bronchoconstriction”
  - ASA sensitive asthmatics, history positive, no challenges
Asthma and Sensitivity to Tartrazine

  - 45 moderately severe asthmatics
    - 50% ASA sensitive
    - 7/45 “reacted” to tartrazine open challenge 20 mg.
    - 0/45 double-blind placebo controlled

  - 54 chronic asthmatic children
  - 50 ASA
  - Double-blind placebo controlled tartrazine challenges
  - none reacted
Asthma and Sensitivity to Tartrazine

- Tarlo and Broder, Clin. Allergy 12:3030, 1982
  - 28 chronic asthmatics
  - 10 ASA sensitive
    - 8 Hx
    - 2 challenge
  - Double-blind placebo controlled
  - 1/28 positive (20.4% decreased FEV1)
    - Not ASA sensitive
    - No response to dietary elimination
Results of Tartrazine Challenges in Known ASA-Sensitive Asthmatics (SCRF)

<table>
<thead>
<tr>
<th>No ASA Sensitive</th>
<th>No. of Tartrazine Challenges (Single Blind)</th>
<th>No of Positive (Single Blind)</th>
<th>No. of Positive Double Blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (1970-1980)</td>
<td>80</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Group II (1981-1985)</td>
<td>70</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Group III (1986-1991)</td>
<td>44</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

194  7  (3.6%)  0
Food Dye and Coloring Act (FD&C) Approved Dyes

- **AZO Dyes**
  - Tartrazine (FD&C Yellow #5)
  - Ponceau (FD&C Red #4)
  - Sunset Yellow #6)
  - Amaranth (FD&C Red #5)

- **Non AZO Dyes**
  - Brilliant Blue (FD&C Blue #1)
  - Erythrosine (FD&C Red #3)
  - Indigotin (FD&C Blue #2)
Commonly Used Sulfiting Agents

- Sulfur Dioxide
- Sodium or Potassium
  - Sulfite
  - Bisulfite
  - Metabisulfite
Possible Mechanisms of Sulfite Sensitivity

- **SO₂ Inhalation**
  - Generated by sulfite in solution
    - Temperature
    - pH
  - Stimulation of cholinergic/irritant receptors

- **IgE Mediated**
  - Anaphylaxis
  - Asthma

- **Sulfite Oxidase Deficiency**

- **Other**
# Relationship of Sulfite Form Ingested and Reactions

<table>
<thead>
<tr>
<th>Food/Beverage</th>
<th>Approx. Sulfite Concentration (ppm SO₂)</th>
<th>Potential for Reaction (Free Sulfite Available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salad</td>
<td>500-700</td>
<td>High</td>
</tr>
<tr>
<td>Dried Fruit</td>
<td>1,000-3,000</td>
<td>High</td>
</tr>
<tr>
<td>Potatoes</td>
<td>100-1,500</td>
<td>Low (but severe)</td>
</tr>
<tr>
<td>Processed/Pkg. Food</td>
<td>&lt;10-1,000</td>
<td>Low (with a few exceptions)</td>
</tr>
<tr>
<td>Wine</td>
<td>50-150</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Monosodium Glutamate (MSG)

Non-essential Dicarboxylic Amino Acid

Purpose: Flavor Enhancement

Dosage: Up to 5 grams: Chinese meal

Reactions: Chinese Restaurant Syndrome

Vascular headache
Monosodium Glutamate (MSG) and Asthma

• Scripps Experience
  – 65 subjects
  – High risk:
    • 50 ASA sensitive asthmatics
    • 15 asthmatics avoiding all MSG
  – Double blind placebo controlled challenges
  – No reactions
  – >95% confidence no association

Woessner et al; *J Allergy Clin Immunol*. 1999; 104: 305.
Monosodium Glutamate (MSG)

Angioedema

Squire; Lancet 1;988, 1987 (letter)

Single-blind placebo controlled challenges (2)

Angiodema 16 hours after ingestion MSG
Aspartame (Nutrasweet®)

Dipeptide (aspartic acid + methyl ester of phenylalanine)

Urticaria

- 2 subjects
- Double-blind placebo controlled
- 25-75 mg Aspartame (6 oz. Diet soft drink)

Headache

- 40 subjects positive history
- One day treatment in hospital
- Negative results

Koehler and Glaros, Headache 28:10, 1988
- 11 subjects positive history
- Four weeks of treatment at home
- Positive results
# BHA / BHT

**Butylated Hydroxy Anisole / Butylated Hydroxy Toluene**

<table>
<thead>
<tr>
<th>Action: Uses:</th>
<th>Antioxidant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast cereals</td>
<td>BHA / BHTBHA</td>
</tr>
<tr>
<td>cake mixes</td>
<td></td>
</tr>
<tr>
<td>chewing gum</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicity:</th>
<th>Nausea, vomiting, cramps, dizziness, confusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEJM 312:648, 1986</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensitivity:</th>
<th>Chronic Idiopathic Urticaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>JACI 86:570, 1990.</td>
<td></td>
</tr>
</tbody>
</table>
## Commonly Used Parabens/Benzoates and Related Chemicals

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl Paraben</td>
<td>Sodium Benzoate</td>
</tr>
<tr>
<td>Propyl Paraben</td>
<td>Hydroxybenzoic Acid</td>
</tr>
<tr>
<td>Benzocaine</td>
<td>Para Amino Benzoic Acid (PABA)</td>
</tr>
<tr>
<td>Procaine</td>
<td></td>
</tr>
</tbody>
</table>
Reaction to Parabens/Benzoates in Asthmatics

  - ASA sensitive asthmatics
  - History positive - no challenges

- Freedman, clin. Allergy 7:407, 1979
  - 14 patients, positive history
  - 4 positive challenges - no placebos

- Weber et al., J. Allergy Clin. Immunol. 64:32, 1979:
  - 43 mod. Severe asthma
  - Double-blind placebo controlled
  - 1/42 reacted - 250 mg. Sodium benzoate
  - 2 years later - negative
Paraben Provoked Anaphylaxis

Local Anesthetics

Aldrete and Johnson, JAMA 207:356, 1969

Corticosteroids

Nagel et al. JAMA 237:1594, 1977

Subjects: Otherwise normal
Reactions: Only to injected paraben
Positive Skin Test: Parabens
Drug with paraben
Passively transferred
Nitrates and Nitrites

Preservatives

Coloring
Flavor
Processed meat

No well documented reports of hypersensitivity reactions

Can provoke vascular headache

Metabolites (Nitrososamines) carcinogenic
Nitrates and Benzoates

• Chronic Pruritis
  – Case Reports: Nitrates \(^1\), \(^2\) or Benzoates \(^3\)
    • All same author
  – Improvement with avoidance
  – Return with reintroduction &/or + challenge
    • pruritis within 24 hours
    • single placebo given first
    • meds withheld

Anaphylaxis From Natural Additives

- Annato, Carmine
- Erythritol
- Spearmint, peppermint, menthol
- Guar gum
- Psyllium
- Carrageenan
- Lupine
- Pectin
- Gelatin
- Mycoprotein
- Celery-Mugwort-Spice
- Lysozyme
Annatto Dye

- Yellow-orange food coloring
- Extracted from seeds of Bixa Orellana tree (South America)
- Common in cheeses
- Anaphylaxis following “Fiber-One” cereal
- + Skin test - no challenge

Carmine

- **Red** food dye
- Extracted from dried female cochineal insects (coccus cacti)
- Anaphylaxis following yogurt, delicatessen meats*, popsicles**, candy, ice cream, pastry, jam, tablets, capsules
- Single case report; + Skin test, leukocyte histamine release - no challenge*
- Single case report; + Skin test, PK test - no challenge **
- 3 patients + skin test; 2 with + blinded placebo controlled challenges

*** Chung, K et al Allergy 2001;56:73-77.
Anaphylaxis From Natural Additives

- Erythritol
  - 4-carbon sugar alcohol
    • prepared from glucose by fermentation
- Used as a sweetener
- May occur naturally in foods such as wine, beer, soy, cheese, mushroom, grape, and watermelon.

Anaphylaxis From Natural Additives

- Spearmint (Mentha spicata)
- Peppermint (Mentha piperita)
- Menthol (Mentha labiateae)
- Flavorings used in chewing gum and toothpaste
- Have been confirmed by challenges to have triggered asthma in two cases

Anaphylaxis From Natural Additives

- Guar gum
- A galactomannan derived from the guar bean
- Used as an emulsifier and binder in foods and pharmaceuticals.
- Severe anaphylaxis and occupational rhinitis/asthma
- + RAST/PST, no oral challenge

Anaphylaxis From Natural Additives

- **Psyllium**
  - Soluble dietary fiber derived from the husks of Plantago ovata seeds.
  - Commonly used in bulk laxatives, and fiber-enriched breakfast cereals.
  - Severe anaphylaxis, occupational asthma/rhinitis
  - Healthcare workers who have prepared and handled psyllium-containing bulk laxatives appear to be at particular risk
  - + RAST tests; no PST, no oral challenges

Anaphylaxis From Natural Additives

• Carrageenan
  – A gelatinous polysaccharide
  – Derived from seaweed
  – Used as a stabilizer and thickener.
  – Anaphylaxis during barium enema
    • Not latex
    • + RAST & PST
    • Pts. abdominal pain resolved on a carageenan free diet

Anaphylaxis From Natural Additives

- Lupine
  - inexpensive flour extender
- Lupine may have some cross-reactivity with peanut.
- Anaphylaxis from a bun with traces of lupine flour
- RAST & PST; + basophil histamine release
- No oral challenge

Anaphylaxis From Natural Additives

- Pectin
- Jelling agent and thickener,
- Cashews, pistachios, citrus (seeds)
- Occupational asthma upon inhalation
- Anaphylaxis upon ingestion
  - 3½ yo “cashew allergy”, anaphylaxis to “fruit smoothie”
  - + RAST, PST, no oral challenge

Anaphylaxis From Natural Additives

- Gelatin
- Anaphylaxis
  - Vaccines
  - Measles, mumps and rubella (MMR), varicella, Japanese encephalitis, influenza (1) has been reported
  - Gummy candies and fruit chews (2)

**Anaphylaxis From Natural Additives**

- **Mycoprotein**
  - Fermented fungus (Fusarium venenatum) bound with egg albumin.
  - Shares common allergenic determinants with other molds.
    - Alternaria, Aspergillus & Cladosporium
  - Used as a meat substitute (marketed as Quorn® in the United States).
  - Allergic reactions mainly in patients with inhalant mold allergy


Anaphylaxis From Natural Additives

- **Celery-Mugwort-Spice Syndrome**
  - Potentially severe form of celery allergy
  - Patients sensitized to both birch and mugwort.
  - React to the Apiaceae family (carrot, caraway, parsley, fennel, coriander, and aniseed), paprika, pepper, mango, garlic, leek, and onion
  - Due to celery profilin (Api g 4), which is highly cross-reactive with profilins from both mugwort (Art v 4) and birch (Bet v 2).
  - Differs from OAS: reactions to **cooked** celery

Angioedema From Natural Additives

• Lysozyme
  – In raw egg, aged cheeses and pharmaceuticals
  – Single case report
  – Positive RAST, prick skin test
  – Negative skin tests and challenges to other ingestants
  – No lysozyme challenge