Adverse Reactions to Food & Drug Additives

Congdon – Allergy Webinar
12/10/25

Ronald A. Simon, MD FACP, FAAAAI, FACAAI

Director, Scripps Allergy Center of Excellence, World Allergy Association
Emeritus Head, Division of Allergy, Asthma & Immunology
Clinical Professor of Medicine, Department of Medicine
Senior Consultant, Division of Allergy, Asthma and Immunology
Scripps Clinic
Adjunct Professor, Dept. of Molecular Medicine
Skaggs Scholar, Dept. of Molecular Medicine
The Scripps Research Institute
La Jolla, CA

1

Objectives

- Following this presentation, attendees should be able to:
  - 1. identify the additives most commonly associated with reactions
  - 2. describe the relationship between food additive sensitivity and conditions like CIU, asthma and hyperactivity/attention deficit disorder
  - 3. evaluate patients who have a history of reactions to food and drug additives

2

Disclosures

- None

3

Definitions

- Food Additive:
  - Basically: any substance added to food.
  - Legally: "any substance the intended use of which results or may reasonably be expected to result (directly or indirectly) in its becoming a component or otherwise affecting the characteristics of any food."
    - This definition includes any substance used in the production, processing, treatment, packaging, transportation or storage of food
- GRAS list
  - An ingredient which has undergone testing and found to be safe now goes on the GRAS list
  - ingredient that has been used commonly before 1958, and in significant quantities, across a large population, and over a sustained period without known harm are considered safe and do not require additional safety evaluations

4

Specific Food Additives

- **Preservatives**
- **Stabilizers**
- **Conditioners**
- **Thickening agents**
- **Sweetening agents**
- **Food coloring**
- **Flavoring agents**
- **Antioxidants**
- **Miscellaneous food additives**

5

Additive Numbers

- First used in ancient Egypt (around 1500 BC)
  - natural extracts added to candies to make them more appealing
- Today > 3,000 FDA approved food additives
  - *https://1wwwfda.gov!foodlingredientspackaging labeling!foodadditivesingredientslucm094211.htm*
- Approx. 1,000 on GRAS list

6

Additives Most Commonly Associated With Adverse Reactions

- FD&C Dyes
  - Tartrazine (FD&C yellow #5)
  - Sunset yellow (FD&C yellow #6)
- 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)

7

Contents of Premarin Tablets (Brown, 0.625mg)

- Methylcellulose 15 CPS
- Talc Titurate
- Lactose
- Magnesium stearate
- Polyethylene glycol 20,000
- Glyceryl mono-oleate
- 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 (Cellulose type material)
- Sodium acetate
- Sodium chloride
- Neutral steroids
- Estrogens

8

Contents of Conjugated Estrogen Tablets (Brown, 0.625mg)

- Methylcellulose 15 CPS
- Talc titurate
- Lactose
- Magnesium stearate
- PEG (Polyethylene glycol 20,000)
- Glyceryl 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 (Polysorbate 80)
- Propyl paraben
- FD&C Yellow #5
- Calcium carbonate
- Tricalcium phosphate
- Soda floc (Cellulose type material)
- Sodium acetate
- Sodium chloride
- Neutral steroids
- Estrogens

9

Tartrazine (FD & C Yellow No. 5)

10

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[1]:
  - 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

Lockey S. Ann Allergy 1959:17;719-725.

11

Additive Challenge Studies in Urticaria and Asthma
Studies With Less Stringent Design Criteria

- Antihistamines/SABA's withheld
- No placebo controls or single placebo given first
- Followed by single doses of multiple additives
- Positive Challenge defined as:
  - Appearance/worsening of urticaria/FEV1 fall a positive reaction
  - Also, unrelated signs a positive reaction
  - Subjective criteria for a positive reaction

12

Challenges in Challenging Patients with Urticaria

- Activity of disease
- Medications
- Controls
- Blinding
- Criteria for a positive reaction

13

Additives in CIU: Conclusions

- With 99% confidence we conclude that sensitivity to any of the 11 food drug additives in patients with CIUA is $\leq$ 1%
- Food/drug additives appear to be a rare cause/exacerbant of CIUA
- Therefore, avoidance is not recommended

14

Challenges in Asthma Patients

- Baseline FEV1>80% predicted (& >1.5L)
- Withhold SABA's
- Continue other meds, including LABA's, if necessary
- Whole day single blind placebo challenge
  - FEV1 drop<10%
- Double blind placebo controlled challenge
- Positive challenge: FEV1 drop>20%

15

Results of Tartrazine Challenges in Known ASA-Sensitive Asthmatics (SCRF)

No ASA Sensitive	No. of Tartrazine Challenges (Single Blind)	No of Positive (Single Blind)	No. of Positive Double Blind
Group I (1970-1980)	80	3	0
Group II (1981-1985)	70	3	0
Group III (1986-1991)	44	1	0
	194	7 (3.6%)	0

16

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)

17

Commonly Used Sulfiting Agents

- Sulfur Dioxide
- Sodium or Potassium
  - Sulfite
  - Bisulfite
  - Metabisulfite
- Has been associated with severe, life threatening asthma attacks
- No longer can be added to foods served as fresh
- Can still be found in wine and dried fruits

18

Monosodium Glutamate (MSG)

Non-essential Dicarboxylic Amino Acid

Purpose:	**Flavor Enhancement**
Dosage:	**Up to 5 grams: Chinese meal**
Reactions:	**Chinese Restaurant Syndrome** **Vascular headache**

19

Monosodium Glutamate (MSG)

Angioedema

Squire; Lancet 1;988, 1987 (letter)

Single-blind placebo controlled challenges (2)

Angiodema 16 hours after ingestion MSG

20

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.

21

Aspartame (Nutrasweet®)

Dipeptide (aspartic acid + methyl ester of phenylalanine)

Urticaria

Kulczycki, Ann. Int. Med 104:207, 1986
- 2 subjects
- Double-blind placebo controlled
- 25-75 mg Aspartame (6 oz. Diet soft drink)

Headache

Schiffman et al. N. Engl. J. Med. 317:1181, 1987
- 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

22

BHA / BHT

Butylated Hydroxy Anisole / Butylated Hydroxy Toluene

Action:	Antioxidant
Uses:	Breakfast cereals cake mixes chewing gum
Toxicity:	Nausea, vomiting, cramps, dizziness, confusion NEJM 312:648, 1986
Sensitivity:	Chronic Idiopathic Urticaria JACI 86:570, 1990.

23

Commonly Used Parabens/Benzoates and Related Chemicals

Methyl Paraben	Sodium Benzoate
Propyl Paraben	Hydroxybenzoic Acid
Benzocaine	Para Amino Benzoic Acid (PABA)
Procaine	

24

Reaction to Parabens/Benzoates in Asthmatics: no convincing positive data

- Samter and Beer, Ann. Int. Med. 68:975, 1968
  - 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

25

Paraben Provoked Anaphylaxis

Local Anesthetics

Aldrete and Johnson, JAMA 207:356, 1969
Latronica et al. Oral Surg 28:439, 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

26

Nitrates and Nitrites

Preservatives

- Coloring
- Flavor
- Processed meat

No well documented reports of hypersensitivity reactions

Can provoke vascular headache

Metabolites (Nitrososamines) carcinogenic

27

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

1. Asero, R J Allergy Clin Immunol 1999;104:1110-1111.
2. Asero, R Clin Exp Derm 2005;30:719-720.
3. Asero, R Allergy 2006;61:1240-1241.

28

Hyperactivity and Artificial Food Colors (AFC's)

29

Hyperactivity and Diet Background Information

- 1973 Dr. Ben Feingold (allergist & pediatrician No CA Kaiser) gives a presentation at annual AMA convention
- 1975 publishes best selling book "Why Your Child is Hyperactive" recommends the "K-P Diet"
  - No sugar, salicylates, preservatives or AFC's
- Neither presentation nor book are "studies"
- Oligoantigenic (K-P) diet studies
  - Initial studies not controlled
  - Initial controlled studies began with responders to oligoantigenic diet then did "DBPC" challenges in diet responders.
    - Multiple dye doses, one placebo.
    - Controls (non ADD HD also responded)
    - Thus controls reacted at the same rate as the hyperactive

Stevens L et al Clin Pediatr 2011;50:279-293

30

Hyperactivity and AFC's Background Information

- 2012 Meta-analysis
- Well-controlled double-blind elimination diets and/or challenge studies of AFC's in patients with ADHD
- There was a small change in parental reports of symptoms
- No significant changes in teacher-reported symptoms were found.

Nigg JT, Lewis K, Edinger T, Falk M. J Am Acad Child Adolesc Psychiatr 2012;51:86-97.e8

31

"Seeing RED"

- Published January 2016
- Center for Science in the Public Interest
- Concluded, AFC's do aggravate ADHD
  - Based on no new data, only the poorly designed studies, anecdotal and patient/family reports
  - Accepting of studies that show a prevalence 1 - 3% in this "high risk" population
  - Seems like coincidence to me

32

Hyperactivity and AFC's Background Information

- AAAAI/ACAAI Food Allergy Practice Parameter 2014
- Summary Statement 21:
  - Clinicians should not recommend food additive avoidance in their patients with hyperactivity/attention deficit disorder. [Strength of recommendation: Strong; A Evidence]
- Upheld the 2010 NIH Food Allergy Expert Panel Report statements

Sampson, HA et al Food allergy: A practice parameter update J Allergy Clin Immunol 2014; 134:1016-1025.

Boyce, JA et. al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel, J Allergy Clin. Immunol. 2010;126: S1-S58.

33

Allergic Reactions From Natural Additives

Anaphylaxis:
Annato, Carmine (colors)
Erythritol (sweetener)
Guar gum (emulsifier and binder)
Psyllium (soluble dietary fiber)
Carrageenan (stabilizer and thickener)
Lupine (inexpensive four extender)
Pectin (thickener) rare cashew allergy (not pistachio)
Gelatin (animal collagen) "chewy"
Mycoprotein (Quorn) (added protein) fermented fungus bound to egg

Celery-Mugwort-Spice
(PFAS: profilin Art v 4 celery (can be cooked) or a defensin Api g 7 mugwort)
Anise, fennel, coriander, cumin, paprika, pepper, and others from the Apiaceae family.
Carrots, peaches, chamomile, mustard, nuts, mango

Lysozyme: angioedema (raw egg, cheeses)

Mints (Lamiaceae) Spearmint, peppermint, menthol (essential oils)
asthma

34

Challenges of the Food Addtive or Chemically Sensitive

- 5 conditions needed to know to perform challenges:
- Type of patient
- Suspect substance
- Type of reaction
- Timing of reaction
- Dose

35

Work-up of the Food Additive Sensitive Patient

- Just like any food allergy patient
  - History, history, history
  - Multiple bonafide reactions related to eating, but not specific food/foods.
  - Maybe multiple bonafide drug reactions too
  - Reactions in restaurants but not at home ("eating organic" and/or "no processed food")
- May be a Multiple Chemical Sensitivity (MCS)/ Idiopathic Environmental Intolerant (IEI) patient
- May be an MCAS patient
- May have underlying neuropsychic issues

36

Challenges of the Food/Additive or Chemically Sensitive

- 5 conditions to perform challenges:
  1. Type of patient: Must be "agreeable", but can be:
     - Normal
     - Histrionic
     - Somatizer
     - Hypochondriacal
     - MCAS; MCS/IEI
- Suspect substance
- Type of reaction
- Timing of reaction
- Dose

37

Challenges of the Food/Additive or Chemically Sensitive

- 5 necessary parameters to perform challenges:
- 1. Type of patient
- 2. Suspect substance
  - Solid
  - Liquid
  - VOC (irritant)
- Type of reaction
- Timing of reaction
- Dose

38

Challenges of the Food/Additive or Chemically Sensitive

- 5 necessary parameters to perform challenges:
- 1. Type of patient
- 2. Suspect substance
- 3. Type of reaction
  - Either objective or subjective
  - Specific
  - Consistent
  - Reproducible
- Timing of reaction
- Dose

39

Challenges of the Food/Additive or Chemically Sensitive

- 5 necessary parameters to perform challenges:
- Type of patient
- Suspect substance
- Type of reaction
- 4. Timing of reaction
  - "Immediate"
  - Minutes
  - Hours
  - Days
- Dose

40

Challenges of the Food/Additive or Chemically Sensitive

- 5 necessary parameters to perform challenges:
- Type of patient
- Suspect substance
- Type of reaction
- Timing of reaction
- 5. Dose
  - Homeopathic
  - Small
  - Large

41

Challenges of the Food/Additive or Chemically Sensitive: Other Design Parameters

- Placebo use
- Duration of challenge
- Blinding
- All of above considered from both MD and patient's perspectives

42

Challenges of the Food/Additive or Chemically Sensitive: Other Design Parameters for the Patient

- Placebo use
  - From MD perspective
    - Always first
    - Always last
    - Always in between
- Dosing and challenge duration
- Blinding

43

Challenges of the Food/Additive or Chemically Sensitive: Other Design Parameters for the Patient

- Placebo use
  - From patient's perspective
    - Can be all
    - Can be none
- Duration
- Blinding

44

Challenges of the Food/Addtive or Chemically Sensitive: Other Design Parameters for the Patient

- Placebo use
- Duration of challenges
  - From MD perspective
    - Whatever reaction history dictates
      - Double the historical reaction time
    - Incorporation of doses
    - Incorporation of placebos
    - May stop challenge early if has already tolerated substance in question
      - May continue to wait for a possible placebo "reaction"
- Blinding

45

Challenges of the Food/Addtive or Chemically Sensitive: Other Design Parameters for the Patient

- Placebo use from MD perspective
- Duration of challenge
  - From patient's perspective
    - Measured in days
      - ½, 1 or more
- Blinding

46

Challenges of the Food/Addtive or Chemically Sensitive: Other Design Parameters for the Patient

- Placebo use from MD perspective
- Duration
- Blinding
  - From MD perspective
    - Oral: "double blind" (to patient and nurse)
    - Inhalational: single blind

47

Challenges of the Food/Addtive or Chemically Sensitive: Other Design Parameters for the Patient

- Placebo use from MD perspective
- Duration
- Blinding
  - From patient perspective
    - Inhalational:
      - consider blindfold
        - » Makes presenting the challenge agents easier
      - nose clip ***ESSENTIAL!***

48

Related Reading

- Bosso JV, Simon RA: Urticaria, angioedema and anaphylaxis provoked by food additives. In: *Food Allergy: Adverse Reactions to Foods and Food Additives,* 4th ed. Metcalfe DD, Sampson HA, Simon RA (eds). Blackwell Scientific Publications, Boston, 2008.

UpToDate: Adverse Reactions to Food Additives; Challenge Study Designs (RAS chapters) Food additives/AFC's in hyperactivity

Andreozzi, L et al Hypersensitivity reactions to food and drug additives: Problem or myth?; Acta Biomed 2019;90:80-90.

Babbel, J et al Adverse reactions to food additives, J Food Allergy 2021;3:8-23. doi 10.2500/jfa.2021.3.210004

49

Questions???

50