PERIOPERATIVE ANAPHYLAXIS: A BRIEF REVIEW

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ADVERSE DRUG REACTIONS (ADR) IN THE PERIOPERATIVE ENVIRONMENT: OVERVIEW

• most perioperative ADR are not allergic
• non-allergic ADR → dose dependent, relatively predictable
  • related to overdose, inadvertent route, drug interaction, side effect, or secondary effect
  • may mimic signs of allergic reaction
• by contrast, allergic reactions in OR are dose independent and unpredictable
In 2641 B.C.E., the Egyptian King Menes died from the bite of a wasp.
PERIOPERATIVE ANAPHYLAXIS*: OVERVIEW

• allergic reactions in OR→causes include drugs, blood products, environmental agents such as skin prep & latex
• anaphylaxis represents the most serious allergic reaction
• diagnosis may be delayed in perioperative environment
• likely causes of perioperative anaphylaxis have evolved over time and exhibit some regional differences
• treatment remains empirical at best
• standardized approach to evaluation often lacking

* literally, anaphylaxis is “backward protection”
ANAPHYLAXIS IS A TYPE I IMMUNE RELATED ALLERGIC REACTION

- Specific IgE elucidated after exposure to allergen
- Receptors attach to basophils and mast cells
- Re-exposure → IgE bridging with degranulation
- First exposure anaphylaxis due to cross-reactivity
BOTH ANAPHYLACTIC AND ANAPHYLACTOID REACTIONS MAY OCCUR PERIOPERATIVELY

- Anaphylactoid reactions are clinically similar to anaphylaxis but mediators are released in absence of IgE.
- \( \sim \frac{2}{3} \) of perioperative allergic reactions are anaphylaxis.

![Diagram](image)
### CHEMICAL MEDIATORS INVOLVED IN ANAPHYLAXIS

<table>
<thead>
<tr>
<th>TIMING</th>
<th>MEDIATORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMEDIATE (PREFORMED)</td>
<td>histamine, proteases, TNF-α, heparin</td>
</tr>
<tr>
<td>MINUTES (LIPIDS)</td>
<td>prostaglandins, leukotrienes</td>
</tr>
<tr>
<td>HOURS (CYTOKINES)</td>
<td>IL-4, IL-13</td>
</tr>
<tr>
<td></td>
<td>immune (%)</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------</td>
</tr>
<tr>
<td>flushing, urticaria</td>
<td>72</td>
</tr>
<tr>
<td>angioedema</td>
<td>12</td>
</tr>
<tr>
<td>bronchospasm</td>
<td>40</td>
</tr>
<tr>
<td>CARDIOVASCULAR</td>
<td></td>
</tr>
<tr>
<td>hypotension</td>
<td>75</td>
</tr>
<tr>
<td>bradycardia</td>
<td>17</td>
</tr>
<tr>
<td>cardiac collapse</td>
<td>1.3</td>
</tr>
<tr>
<td>cardiac arrest</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

MERTES ET AL 2003
A RARE EVENT → HIGH INDEX SUSPICION REQUIRED TO PREVENT MORBIDITY

• incidence 1:3500-20,000* → most anesthesiologists will witness only a few such reactions in a lifetime
  ▪ mortality 3-4%  CNS sequelae 5-6%

• Jacobsen et al 2001¹
  ▪ simulator study: 0 of 42 anesthesiologists made the correct dx during the first 10 minutes of anaphylaxis

¹ ACTA ANAESTHESIOLOGICA SCANDINAVICA 2001;45:315
* Anesth Analg 2003;97:1381
INITIAL CLINICAL MANIFESTATIONS OF ALLERGIC REACTION MAY BE MISSED

- most common are CV and cutaneous BUT
- CV ↓ common after anesthesia induction
- and cutaneous signs may be missed due to draping of the patient
SUSPECTED ANAPHYLAXIS: PRIMARY TREATMENT

• remove exposure; decrease or remove anesthetic
• ABC’s
  • 100% oxygen and definitive airway support
  • volume expansion (25-50 ml/kg)
• epinephrine (titrate infusion, as needed)
  • 0.1 μg/kg hypotension and 1 μg/kg cardiac collapse
  • $\alpha_1$ effects support BP and $\beta_2$ effects bronchodilate
SUSPECTED ANAPHYLAXIS: SECONDARY TREATMENT

- H-1 and H-2 blockers
- bronchodilators as needed
- corticosteroids (0.5-1 mg/kg methyprednisolone)
- supportive ICU care
- tryptase level within 2 hours; definitive in-vitro (RAST) or in-vivo (skin, intradermal) allergy testing recommended
  - skin test deferred 4-6 wks due to mediator depletion
ROLE OF VASOPRESSIN IN REFRACTORY ANAPHYLACTIC SHOCK

• 6 case reports of shock unresponsive to “standard” therapy with epinephrine / fluid and steroid
• 2 units vasopressin stabilized all 6 patients
• vasoconstriction ↑ in skin, SSM, intestine and fat, less coronary renal vasoconstriction, cerebral vasodilatation
• accompanying editorial → therapies for anaphylaxis are class C or D at best (Cochrane criteria); so in refractory shock, vasopressin is as indicated as any other Rx

SCHUMMER C. ANESTH ANALG 2008;107:620
### Evolving Causes of Perioperative Anaphylaxis: I (France 1984-1989)

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>muscle relaxants</td>
<td>81</td>
</tr>
<tr>
<td>natural rubber latex</td>
<td>0.5</td>
</tr>
<tr>
<td>antibiotics</td>
<td>2</td>
</tr>
<tr>
<td>hypnotics</td>
<td>11</td>
</tr>
<tr>
<td>colloids</td>
<td>0.5</td>
</tr>
<tr>
<td>opioids</td>
<td>3</td>
</tr>
<tr>
<td>other</td>
<td>2</td>
</tr>
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</table>

Gurrieri C. Anesth Analg 2011;113:1202
### EVOLVING CAUSES OF PERIOPERATIVE ANAPHYLAXIS: II (FRANCE 1992-1994)

<table>
<thead>
<tr>
<th>ALLERGEN</th>
<th>INCIDENCE (%)</th>
</tr>
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<tbody>
<tr>
<td>muscle relaxants</td>
<td>59.2</td>
</tr>
<tr>
<td>natural rubber latex ***</td>
<td>19</td>
</tr>
<tr>
<td>antibiotics</td>
<td>3.1</td>
</tr>
<tr>
<td>hypnotics</td>
<td>8</td>
</tr>
<tr>
<td>colloids</td>
<td>5</td>
</tr>
<tr>
<td>opioids</td>
<td>3.5</td>
</tr>
<tr>
<td>other</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*** marked increase

LAXENAIRE. ANN FR ANESTH REANIM 1996;15:1211
# EVOLVING CAUSES OF PERIOPERATIVE ANAPHYLAXIS: III (FRANCE 1999-2000)

<table>
<thead>
<tr>
<th>ALLERGEN</th>
<th>INCIDENCE (%)</th>
</tr>
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<tbody>
<tr>
<td>muscle relaxants</td>
<td>58.2</td>
</tr>
<tr>
<td>natural rubber latex</td>
<td>16.7</td>
</tr>
<tr>
<td>antibiotics ***</td>
<td>15</td>
</tr>
<tr>
<td>hypnotics</td>
<td>3.7</td>
</tr>
<tr>
<td>colloids</td>
<td>2.7</td>
</tr>
<tr>
<td>opioids</td>
<td>1.4</td>
</tr>
<tr>
<td>other</td>
<td>2.9</td>
</tr>
</tbody>
</table>

*** marked increase

MERTES. ANESTHESIOLOGY 2003; 99:521
PERIOPERATIVE ALLERGIC REACTIONS
MAYO CLINIC DATA BASE 1992-2010 (I)

- retrospective data base postoperative referrals for allergy testing

- clinical presentation consistent with immediate-type allergic reaction

- Ig-E
  + skin test
  ↑ tryptase
  N = 18

- non Ig-E
  - skin test
  ↑ tryptase
  N = 6

- possible non Ig-E
  - skin test
  tryptase either nl or not obtained
  N = 14

- maintenance 74%
  induction 18%
  PACU 8%

- 38 patients (20 female)
  1:34,000 incidence

GURRIERI C. ANESTH ANALG 2011;113:1202
• causative agent NOT identified in 53% of cases

<table>
<thead>
<tr>
<th>+ SKIN TEST (18 patients)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>antibiotics</td>
<td></td>
</tr>
<tr>
<td>cefazolin</td>
<td>9 (50)</td>
</tr>
<tr>
<td>levofloxacin / ampicillin</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>neuromuscular blockers</td>
<td></td>
</tr>
<tr>
<td>vecuronium, succinylcholine</td>
<td>2 (11)</td>
</tr>
<tr>
<td>latex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (17)</td>
</tr>
<tr>
<td>other / multiple</td>
<td></td>
</tr>
<tr>
<td>propofol; isosulfan blue; midazolam; fentanyl;</td>
<td>4 (22)</td>
</tr>
<tr>
<td>flumazenil</td>
<td></td>
</tr>
</tbody>
</table>
PERIOPERATIVE ALLERGIC REACTIONS
MAYO CLINIC 1992-2010 (III): OBSERVATIONS

• though causative agent often lacking, unlike European studies, antibiotics >cause of anaphylaxis than NMB’s
  • different testing methods ?? vs. geographical differences

• opioids rare cause, in contrast to Danish study (Garvey)

• severity of rxns: 58% abortion of case / 40% ICU

• elevation of tryptase (t ½ 2 hours) depends on sampling

• lack of causative agents in > 50% suggests need for standardized protocols to investigate anaphylaxis
MUSCLE RELAXANTS & ANAPHYLAXIS

- sux > benzylisoquinolium > aminosteroid
  - histamine release w/benzylisoquilium compounds such as atracurium is not immune mediated
- IgE to 4° or 3° ammonium ions mediate anaphylaxis
  - prior sensitization may be due to OTC meds, cosmetics, foods
- cross-sensitivity between muscle relaxants in 60%
- rocuronium ↑ incidence anaphylaxis in Norway, but not in US; may represent false + testing vs. population based differences in sensitization
NATURAL RUBBER LATEX AND ANAPHYLAXIS

• milky sap produced by *Hevea brasiliensis* tree
• frequent exposures to latex in the OR, although many OR environments now going latex-free.... as a result →
• incidence ↓ but still probably ~ 10% periop anaphylaxis
• increased risk health care workers, spina bifida, G-U anomalies, rubber workers, patients with atopy / eczema
• certain food allergies (banana, kiwi, avocado) associated
• lipid vehicle w/soybean oil, egg lecithin and glycerol
  • egg lecithin from yolk; most egg allergy related to ovalbumin in egg white / -ve allergy testing w/propofol in 25 pts with egg allergy

• Laxenaire: 2.1% of perioperative anaphylaxis; most Ig-E related
  • sensitization from isopropyl groups in dermatologic products

• estimated incidence in French study 1:60,000
  • compares favorably to 1:30,000 incidence with thiopental

• bottom line – “safe” in egg allergy but is allergenic and could be increased incidence if atopy, multiple food allergies
ANTIBIOTICS AND ANAPHYLAXIS

• Mayo series, antibiotics → 50% IgE-mediated anaphylaxis
  • cephalosporins caused majority of these

• PCN most common cause anaphylaxis in US overall (75% anaphylactic deaths) but only 10-20% PCN allergy is true

• cross-sensitivity between PCN and cephalosporins reported (∼10%); usually non-immunologic rash, most authors “OK” with cephalosporins unless PCN allergy true anaphylaxis

• recommend that antibiotics be given prior to other agents to facilitate diagnosis should allergic reaction occur
PERIOPERATIVE ANAPHYLAXIS: FINAL OBSERVATIONS

• myriad exposures in the perioperative environment
  • IV drugs, blood products, contrast, latex, colloids
  • NMB’s and antibiotics most likely causes at present time

• allergic reaction may occur on 1st exposure

• when in doubt, discontinue latex

• recommend: standardized protocols to test all agents administered during anesthesia, including medications and occult antigens such as latex and chlorhexidine