Anaphylaxis: What Every Anesthetist Should Know….

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Nurse Anesthesia Program
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Participants will:

1. Describe the epidemiology of anaphylactic reactions during anesthesia.
2. Differentiate between anaphylactic and anaphylactoid responses
3. Discuss the clinical presentation of anaphylaxis during anesthesia.
4. Identify agents used during local, regional, or general anesthesia most likely to precipitate an anaphylactic reaction.
5. Prioritize treatment interventions during perioperative anaphylactic reactions according to patient presentation.

Content Outline:

1. Epidemiology of Anaphylactic Reactions
2. Components of the Anaphylactic Reaction
3. Clinical Presentation of Anaphylaxis
4. Differentiation of Anaphylaxis and Anaphylactoid Reactions
5. Important Lab Markers of Anaphylaxis
6. Triggers during the Perioperative Period
7. New and Traditional Treatment of Anaphylaxis
8. Conclusion
Anaphylaxis: What Every CRNA Should Know....

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(Winter Institute for Simulation Education and Research)

Anaphylaxis

- Multiple medication reactions associated with the term
  - Significant confusion in the literature

- One definition?
  - “a clinical syndrome characterized by acute cardiopulmonary collapse following antigen (foreign substance) exposure”

- Definition is broadening – American Association of Allergists and Immunologists


Why More?? Unknown But Two Possible Explanations

- Exposure theory
  - Modern life has resulted in exposure to many more pollutants and antigens
  - 95% of time for most Americans is indoors

- Sanitized environment theory
  - The world around us and our children is far cleaner than ever before in history
  - We pasteurize and sanitize everything
  - Therefore- reduced exposures- failure of immune system to develop ‘desensitization’ to some antigens and over-reaction to later exposures

Increasing Incidence of Food Allergy

- Teen Dies from Kissing Boyfriend
  - Ref paper: USA Today, Nov. 29, 2005

- Residual peanut antigen in saliva

- ~ 150-200 anaphylactic food deaths in US
  - Increasingly rapidly
    - Today Show, November 30, 2005

History

Epidemiology & Anaphylaxis

Components of the Reaction

Anaphylactic vs. Anaphylactoid Clinical Presentation

Lab Markers

Perioperative Triggers

Treatment

History

- 1st Case??
  - Tomb of King Menes of Egypt: Wasp sting: 2640 BC

- 1902: Portier/Richet
  - Sea anemone toxin in dogs
  - Greek: Ana (against), Phylaxis (protection)

- 1913:
  - Richet receives the Nobel Prize in Physiology for his collaborative research with Portier

- 1967:
  - Ishikaza et al.: IgE discovered

- 1975:
  - Coombs/Gell: hypersensitivity reaction classification
Classification of Immune Reactions

- **Type I:**
  - IgE (IgG) reactions: immediate hypersensitivity
- **Type II:**
  - Antibody dependent, cytotoxic
- **Type III:**
  - Immune complex reactions: complement activated
- **Type IV:**
  - T-cell mediated: contact dermatitis (glove related)
  - Common
  - Organ rejection: host vs. graft or graft vs. host diseases

Coombs and Gell, 1975: classification of hypersensitivity reactions

Variance in Perioperative Incidence

- Skewing with higher incidence of reaction related to muscle relaxants?
  - Sample characteristics/study design?
    - Size
    - Women > men (as many as 70% of cases - all causes)
    - Age
    - Genetics
    - Under-reporting?
    - Diagnostic capability?

Laxenaire MC, Mertes PM, Moess J. Anaphylactic and Anaphylactoid Reactions During Anesthesia: Advancing Knowledge in Healthcare & McMahon Publishing; 2004

Anaphylaxis in the ‘World’

- Anaphylaxis reported to represent 0.02% of all ER admissions
  - Idiopathic event: ~ 50% of cases
  - Food: peanuts and shellfish
  - ~ 10,000 events
  - Drugs:
    - Antibiotics and NSAIDs
    - Bee or wasp stings
    - Radiocontrast media
    - Latex
- Incidence in ALL inpatients of ~ 1: 3000

What is the true incidence of perioperative anaphylaxis?

Asthma and anaphylaxis - a statistical challenge

Rocuronium and anaphylaxis - a statistical challenge

Perioperative Anaphylaxis

- Represents ~10% of anesthetic complications
- Incidence reported as 1:1,000 to 1:25,000 anesthetics... Why the disparity?


Statistical Problem With Rare Events

- (Graph showing distribution of events with rare events indicated)

Annual Mortality Estimates for Specific Agents: Overall US

- **Anaphylactic**
  - Food: 150-200/yr
  - IV PCN: 100-500/yr
  - Stinging insects: 40-100/yr.

- **Anaphylactoid**
  - RCM: < 500/yr
  - NSAIDS?

Components of Reaction

- **Antigen**
  - Protein, large, MW>8000
  - Regularly occurring molecular groupings

- **Hapten**
  - Smaller molecules (drugs, chemicals, etc)
  - Attached to endogenous protein

- **Leukocytes = Basis of intrinsic immunity**

- **Lymphocytes = Basis of acquired immunity**

- **Antibodies**

Perioperative Mortality Rate?

- **Mortality remains significant- as high as 3.4-6.0% of cases of anaphylaxis...Why?**

- Perhaps simulation science can provide some clues....
  - In one study, none of 42 anesthesiologists tested on a high fidelity simulator made the correct diagnosis within the first ten minutes

- **Upon recognition, the majority did not implement a structured plan of treatment**

Leukocytes: Intrinsic Immunity

<table>
<thead>
<tr>
<th>Types</th>
<th>#/ml (gauge)</th>
<th>%</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocyte:</td>
<td>3000-6000</td>
<td>55.65</td>
<td>Bacteria/virus defense</td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td></td>
<td>Phagocytes</td>
</tr>
<tr>
<td>Granulocyte:</td>
<td>0-300</td>
<td>1-3</td>
<td>Parasite defense</td>
</tr>
<tr>
<td>Eosinophils</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulocyte:</td>
<td>0-100</td>
<td>0.1</td>
<td>Concentrated in perivascular tissues. Granules: mediators</td>
</tr>
<tr>
<td>Basophil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mast cell</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocyte</td>
<td>300-500</td>
<td>3-6</td>
<td>Phagocytes, R-E system</td>
</tr>
<tr>
<td>Lymphocyte (B &amp; T)</td>
<td>1500-3500</td>
<td>25-35</td>
<td>Humoral cellular immunity.</td>
</tr>
<tr>
<td>Plasma cell</td>
<td>?</td>
<td>?</td>
<td>ATB factories. From B lymphocytes</td>
</tr>
</tbody>
</table>

How Common is Allergy to Anesthetic Agents Overall- August 2006?

- **Tomayo E et al. Allergy 2006;61:952-953**
  - Prospective trial- N=424
  - Skin prick testing for 30 anesthetics
  - 4.7% had at least one positive
  - Muscle relaxants were #1
  - Previous history of drug allergy was the only predictor

Lymphocytes: Acquired Immunity

<table>
<thead>
<tr>
<th>B Cells</th>
<th>T Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral Immunity(Blood)</td>
<td>Tissue Immunity/Cellular</td>
</tr>
<tr>
<td>Origin: Stem cells</td>
<td>Origin: Stem cells</td>
</tr>
<tr>
<td>Processed: Bursal equivalent</td>
<td>Processed: Thymus</td>
</tr>
<tr>
<td>Stored: Lymph tissue sites</td>
<td>Stored: Lymph tissue sites</td>
</tr>
<tr>
<td>Antigen contact:</td>
<td>Antigen Contact:</td>
</tr>
<tr>
<td>Activated: T helper.</td>
<td>Helper T gives off lymphokines, activates B cells.</td>
</tr>
<tr>
<td>Plasma Cell:</td>
<td>Cytotoxic and suppressor T’s are activated.</td>
</tr>
<tr>
<td>Makes antigen specific antibodies</td>
<td>T’s develop antigen specific receptors.</td>
</tr>
<tr>
<td>Clones: amplification</td>
<td>T memory cells stored in lymph tissue</td>
</tr>
<tr>
<td>Clones: become B memory cells that remain in lymph tissue</td>
<td></td>
</tr>
</tbody>
</table>
Anaphylactic Response & Antibody Formation

- Initial contact
  - Sensitization of cellular/humoral components
- 2nd exposure = ↑ degranulation of mast cells..... Why?
  - Mast cells have 40-100,000 IgE attachment sites
  - Antigen must cross bridge two adjacent IgE antibodies to degranulate
  - ↑ allergy history = vast ↑ IgE sites

Antibodies

- Serum glycoproteins produced by plasma cells(humoral)
- Attach to immune cells and spray antigen with contents
- Activate the complement system
  - Cascade: amplifies the response
  - C3A, C4A, C5A

Antigen Presenting Cell to Degranulation

Are all mast cells alike?

Are they essentially the same cells as basophils aside from location?

Yoshino A. Nagashima S. Uchiyama M.


- Anaphylactoid reaction in a surgeon to surgical rubber
  - Do not differentiate the terminology
  - No previous symptoms
  - Full blown reaction requiring resuscitation

Why the Confusion of Terms?

- Anaphylaxis
  - IgE mediated
  - Indirect mast cell effect
  - Antigen-antibody response results in mast cell/basophil degranulation, mediator release
- Anaphylactoid
  - Direct mast cell degranulation as a result of the chemical structure of drug
  - IgE cannot be implicated
    - May be less severe
Which is Which?

An **Anaphylactoid** reaction *may* be less profound, however, it cannot be **clinically distinguished** from an **Anaphylactic** reaction.

Other Immunologic: Non-Anaphylactic

- Non-IgE mediated but identical symptom complex
- A variety of substances which activate *complement* which then activates neutrophils
  - Complement fragments are considered to be anaphylactoxins
  - Histamine and a variety of other mediators are released from mast cells
- Identical presentation

Symptoms During Anesthesia

- **Most common: circulatory collapse**
  - Most common symptom during GETA (49%)
  - Sympathoadrenergic responses may be blunted
  - Tachycardia may not be present
- **SAB / Epidural = sympathectomy**
  - Therapy may need to be even *more* aggressive

**Onset, Duration, Severity**

- **True anaphylaxis has a *fast onset***
  - Typically < 5 min in the perioperative setting
  - Depends on exposure route and patient
- **Duration and severity of response is multifactorial (can last >24 hr)**
  - Atopy / anxiety/ other variables
  - Time sequence of previous exposure
- **Does dose matter?**
Perioperative Diagnosis

- More difficult - why?
  - Loss of subjective complaints (signs)
  - Absence of cutaneous clues (draping)
  - Use of multiple drugs (masking)
- Overdependence on technology??
  - That pressure can’t be right - can it??

Symptoms: Awake vs. Asleep

<table>
<thead>
<tr>
<th>System</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>Pruritus, urticaria, angioedema</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, dysrhythmias, pulmonary hypertension, decreased SVR, cardiovascular collapse, cardiac arrest</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Cyanosis, rhinorrhea, shortness of breath, increased ETCO₂, respiratory failure, bronchospasm, acute pulmonary edema, increased peak airway pressure</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>Confusion, agitation, decreased level of consciousness, sense of impending doom (angor ani)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>DIC</td>
</tr>
<tr>
<td>Renal</td>
<td>Decreased renal output secondary to tubular secretion</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, diarrhea, cramping</td>
</tr>
</tbody>
</table>

Table 1. Possible manifestations of anaphylactic reactions in the perioperative setting


Testing for Allergy

- In Vivo
  - Skin Prick Test (epidermal)
  - Intradermal test
  - Bronchial challenge
  - Scratch test
  - Patch test
- In Vitro
  - RAST/Elisa
  - Serum IgE assays
  - Complement C3-C5
  - Serum Tryptase levels
  - 40-60 min peak
  - Carboxypeptidase**

Mortality: General vs. Perioperative

In fatalities: > 50% die within the 1st hour

Most common perioperative (recognized) presenting sign is cardiovascular collapse

Testing Table

<table>
<thead>
<tr>
<th>Test</th>
<th>Time Frame</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin Prick Test (epidermal)</td>
<td>0-5 min after antigen</td>
<td>Serum IgE, mast cell antigen release</td>
</tr>
<tr>
<td>Bronchial challenge</td>
<td>0-60 min after antigen</td>
<td>Lung histamine release</td>
</tr>
<tr>
<td>Scratch test/Patch test</td>
<td>0-24 hours after antigen</td>
<td>Skin histamine release</td>
</tr>
<tr>
<td>Complement C3/C5</td>
<td>24-48 hours after antigen</td>
<td>Serum IgE, mast cell antigen release</td>
</tr>
<tr>
<td>IgE antibody (RAST)</td>
<td>24-48 hours after antigen</td>
<td>Serum IgE, mast cell antigen release</td>
</tr>
<tr>
<td>Carboxypeptidase</td>
<td>24-48 hours after antigen</td>
<td>Serum IgE, mast cell antigen release</td>
</tr>
</tbody>
</table>

Table: O’Donnell JM. Current Reviews in Anesthesiology-manuscript


Carboxypeptidase: Is electrocardiogram as which tryptase is not deleted.
Testing Risks

- Clinical challenges???!
  - Out on a limb...way out
  - In vivo vs. in vitro safety

- Novembre E et al. Skin-prick-test-induced anaphylaxis. *Allergy*. 50, 6, 1995;511-513

Initiating Perioperative Agents

- Muscle relaxants:
  - 50-70% of cases!
    - Also #1 anaphylactoid
    - Quaternary amines
      - Soaps, perfumes, makeup sensitize
  - Latex:
    - Special populations

- ATB:
  - PCN
    - Most frequent anaphylactic in general population at ~3%
  - Vancomycin
    - #1 anaphylactoid ATB
  - Cephalosporins
  - Hypnotics
    - Propofol/STP

Agents involved (%) in anaphylaxis during anesthesia in France (n = 477) from January 1997 to December 1998.
Muscle Relaxant Anaphylaxis

<table>
<thead>
<tr>
<th>Muscle relaxant</th>
<th>25 years (1980-2004): cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>1,437</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>905</td>
</tr>
<tr>
<td>Atracurium</td>
<td>475</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>281</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>397</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>40</td>
</tr>
<tr>
<td>Gislatracurium</td>
<td>11</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
</tr>
</tbody>
</table>


Contrast Media

- Usually anaphylactoid
- Adverse reactions
  - 1-3% with non-ionic
  - 5-12% with ionic
- Severe reactions rare
  - Mortality 0.9:100,000


Patients with True MR Allergy

Possible Choices

- Avoidance when possible
  - Regional anesthesia
- Monovalent hapten therapy
  - Molecules with only 1 quaternary group may be one treatment.
  - Would run as infusion


Perioperative Triggers

- Colloids
  - Dextran/Hetastarch
  - T & C blood (~3%)
- Opioids
  - MSO4 = probably anaphylactoid
- Others
  - Ester locals (PABA)
  - Chymopapain
  - Aprotinin
  - Protamine (NPH)
    - Purified pork and humanin have ↓
    - Radiocontrast media
      - Ionic vs. non-ionic
- Airway
  - 100% O2
  - Intubate if indicated: Use muscle relaxant?
- Epinephrine
  - Dose: Dependent on symptoms
    - Mast cell effects, alpha effect, beta effects
- Fluids: Aggressively replace
  - *Loss of 40-50% of IV volume
  - 2-4 liters of balanced solution

Hepner DL, Castells MC. Anaphylaxis During the Perioperative Period Anesth Analg 2003;97:1381–95
Vervloet D, Magnan A, Birnbaum J, Pradal M. Allergic emergencies seen in surgical suites. Clinical Reviews in Allergy and Immunology 1988;495-47

Choice of Epinephrine Route/Dose

- **IV**
  - Severe symptoms
  - Dose Range: 0.1mcg/kg to large doses in severe reactions
- **SQ vs. IM**
  - Emergent reaction...
  - Dose: 100-500 mcg (0.1 to 0.5 mg)
- **Sublingual??**

Caution IS Warranted...

- **CV**: MI, heart failure etc...
- **Case Report:**

Vastus Lateralis via Blue-Jean

- IM route has been demonstrated to be clearly superior with respect to efficacy.


Caution vs Urgency of Giving Epi

- **Pumphrey-2000**
  - 92-98
  - 168 anaphylaxis deaths in UK from all causes
  - 3 were due to epi overdose
  - Epinephrine was used in 62% of cases but only 14% of the time before cardiac arrest
  - Compares with 11% in recent US Study
  - (AAAI 2006)


20 Treatment or Pre-Treatment

- **Other inotropes or infusions**
  - Vasopressin
  - Albuterol
    - β2 agonism
  - Corticosteroids
  - Glucagon
  - Atropine
  - H1/2 antagonism


Epinephrine Is Critical

However......
Problems With Giving $H_{1,2,3}$ Antagonists During Anaphylaxis?

- Administer both $H_1$ and $H_2$ blockers in treating anaphylaxis to balance effect?

**Histamine H3 Receptor Blockade Improves Cardiac Function in Canine Anaphylaxis**

CHAIR CHEUNG, SATYENDRA SHARMA, HARJEET UMSRI, EDGAR BAUTISTA, KERI DUKE, JULIAN BECKER, WAYNE KERPOS, and STEVEN M. HAIN

Department of Medicine, Section of Respiratory Disease and Critical Care Medicine, Department of Medicine, Section of Respiratory Medicine, Department of Anesthesiology and Pain Medicine, Section of Thoracic Surgery, and Department of Pediatrics, University of Manitoba, Winnipeg, Manitoba, Canada

**Should We Give Histamine Blockers?**

![Diagram showing Normal CA vessel with H1 and H2 effects](image)

**Beta Blockers and Increased Risk?**

- Javeed N. et al. 1996:
  - Case analysis:
    - 52 yo male for cardiac cath, on B blockers
    - Pretreated with steroid, Benadryl then RCM given
    - Severe reaction: aggressive therapy, finally responded to glucagon, NE, DA
  - B blockers:
    - Theory: may increase mediator release?
    - Interfere with epi effectiveness
    - Consider glucagon and atropine

**Biphasic Responses/Recurrence**

- 1-20% of cases*
  - Lee, 2000, found a 6% incidence in 108 pediatric cases.
  - Occur 1-8 (as far out as 24) hours after symptoms seem to resolve
  - Argues for post-response monitoring and admission to ICU

**Take Home on Histamine Blockers**

- $H_1$ receptor blockers have demonstrated efficacy
- $H_2$ receptor blockers are not recommended in management of acute anaphylaxis
  - If given alone, may precipitate vasoconstriction
  - May have cross reactivity for $H_3$ – danger of unopposed sympathetic outflow → cardiac ischemia

**Questions/Comments**