The Not-So-Gentle Summer Febreze

Omar Malas MD

Practical Updates in Anesthesiology, February 4th, 2020

Department of Anesthesiology

Michigan Medicine
Disclosures

• None
Case

- 74 yo 84kg Male presents for segment IVb/V partial hepatectomy
- PMHx: cholangiocarcinoma s/p chemotherapy, COPD, Type II DM, HTN
- PSHx: Bilateral cataract extraction, liver biopsy, L subclavian central venous port placement

Case

• Meds: Aspirin 81mg qday, Metformin 500mg BID, Metoprolol succinate 75mg qday, simvastatin 20mg qday

• Allergies: None

• SHx: Former smoker, Quit 2002 (30 pack-year), former EtOH abuse, quit 1972
Perioperative Course

• Pre-operative management
  • T7/8 thoracic epidural, no complications
  • Right radial A-line

• Induction
  • Fentanyl 50mcg, lidocaine 60mg, propofol 120mg, rocuronium 70mg
  • Grade 2M, 2a view with Mac 4 VL, 8.0mm ETT at 22cm
  • 16g and 14g placed

• Maintenance
  • Isoflurane at 0.8-1 MAC, intermittent fentanyl and rocuronium boluses
  • Goals: judicious fluid management, low CVP to decrease bleeding
Intraoperative Course

• 1030 – 1130: Relieved for lecture
• 1110: Surgical resection complete, 600cc IV fluids given
• 1130: Midway through closing, hemodynamically stable, estimated blood loss 850cc, IV fluids 1800cc
• 1136: Surgical dressing complete, pt has 1/4 TOF
• 1137: 4mg/kg (360mg) Sugammadex given
Hemodynamic Collapse

• 1139:
  • A-line reading 41/30 mmHg, no pulse oximetry reading
  • A-line transducer appropriately positioned
  • No femoral or carotid pulses palpable
Differential Diagnosis

- STEMI/NSTEMI
- PE
- Venous air embolism
- **Anaphylaxis**
- Epidural bolus
- Hemorrhage
- Neurogenic shock
- Respiratory arrest
- Pneumothorax
- Sepsis

- Dysrhythmia
- Medication overdose/error
- Hypoglycemia
- Pulmonary HTN
- Severe MR
- Ventricular septal rupture
- Ventricular free wall rupture
- Chordae tendineae or papillary muscle rupture
- Cardiac tamponade
Outline

I. Case Introduction

II. Anaphylaxis
   I. Definition
   II. Pathophysiology
   III. Diagnosis
   IV. Causal Agents
   V. OR considerations
   VI. Severity
   VII. Treatment

III. Sugammadex
   I. Brief history
   II. Anaphylactic incidence
   III. Cross reactivity

IV. Case Finale

V. Questions
Anaphylaxis – Definition

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death."
Anaphylaxis – Pathophysiology

• Allergic reactions: IgE, complement, nonimmunologic mast cell activation

• Initial exposure
  • IgE antibodies produced by B cells in response to allergen
  • Clinically silent

Anaphylaxis – Pathophysiology

Ali MR. Anaphylaxis. Slideshare.net. 2015; accessed 9/18/18
Anaphylaxis – Pathophysiology

• Subsequent exposure
  • Cross-linking of IgE $\rightarrow$ release of intracellular cytokines, chemokines, leukotrienes, histamine, and inflammatory mediators
    • Histamine $\rightarrow$ bronchospasm, urticaria, angioedema, hypotension, diarrhea
    • Tryptase $\rightarrow$ recruitment of the complement cascade; further mast cell degranulation
    • NO $\rightarrow$ Contributes to hypotension; some antagonism of bronchospasm
    • Factor XII $\rightarrow$ clotting and disseminated intravascular coagulation (DIC)
    • Proteoglycans (heparin) $\rightarrow$ recruitment of kinins (worsen vasodilation and vascular permeability); contribute to DIC
    • TNF-α $\rightarrow$ increased vascular permeability and vasodilation
    • C4, D4, E4 $\rightarrow$ smooth muscle contraction, vasodilation, increased vascular permeability
    • IL9, IL13 $\rightarrow$ airway hyperresponsiveness
    • IL4, IL9, IL13 $\rightarrow$ overproduction of mucus

# Anaphylactic vs Anaphylactoid Reactions

<table>
<thead>
<tr>
<th></th>
<th>Anaphylactic</th>
<th>Anaphylactoid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>IgE-mediated mast cell activation</td>
<td>Complement-mediated direct mast cell activation</td>
</tr>
<tr>
<td><strong>Clinical Presentation</strong></td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td><strong>Clinical Manifestation</strong></td>
<td>More severe*</td>
<td>Less severe*</td>
</tr>
<tr>
<td><strong>Histamine</strong></td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td><strong>Tryptase</strong></td>
<td>Elevated</td>
<td>Elevated or unchanged</td>
</tr>
<tr>
<td><strong>Specific IgE assays</strong></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Sensitization required?</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Intradermal Skin testing</strong></td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Anaphylaxis – Clinical Features

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical Features</th>
<th>Differential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocutaneous</td>
<td>Pruritus, flushing, erythema, acute urticaria, angioedema</td>
<td>Carcinoid syndrome, contact or cholinergic urticaria, medication-induced vasoconstriction</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Laryngeal edema, hoarseness, bronchospasm, hypersecretion, increased peak airway pressure, decreased O₂ saturation</td>
<td>Malignant hyperthermia, asthma, aspiration, mucous plug, mainstem intubation, recurrent laryngeal nerve injury, post-extubation stridor</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>(Pre)eyscope, tachycardia/bradycardia, hypotension, dysrhythmia, cardiovascular collapse, cardiac arrest</td>
<td>Vasovagal reaction, arrhythmia, MI, PE, tension pneumothorax, tamponade, shock</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Disseminated intravascular coagulation (DIC)</td>
<td>Transfusion reaction, hemorrhage</td>
</tr>
</tbody>
</table>
Anaphylaxis – Diagnosis

TABLE I. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   
   AND AT LEAST ONE OF THE FOLLOWING
   
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

Anaphylaxis – Diagnosis

1. Unknown allergen for that patient

2. Known allergen for that patient

Anaphylaxis – Causal Agents

- Overall incidence between 1:3500 and 1:20,000 anesthetics
  - Female predominant (2:1)
- Neuromuscular blocking agents (NMBA)
  - 50-70% of periop anaphylaxis
  - Quaternary ammonium → IgE mediated reaction
  - Benzylisoquinolines → non-IgE mediated reactions
- Natural rubber latex
  - 5-15% of periop anaphylaxis
- Antibiotics
  - Up to 15% of periop anaphylaxis
  - Penicillins and cephalosporins responsible for 70% of periop anaphylaxis from antibiotics
Anaphylaxis – OR Considerations

• Signs and symptoms may be masked by OR circumstances

• Tachycardia
  • Masked by cholinergic drugs, beta blockers, bradycardia associated with GA

• Hypotension
  • Blamed on induction agents, opioids, beta blockers, NMBAs

• Urticaria
  • May be missed as patient is covered by drapes

• Respiratory: laryngeal edema, cough, bronchospasm
  • Masked by intubation and mechanical ventilation

## Anaphylaxis – Severity

<table>
<thead>
<tr>
<th>Class</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Generalised cutaneous signs (erythema, urticaria with or without angioedema)</td>
</tr>
<tr>
<td>II</td>
<td>Moderate multiorgan involvement with cutaneous signs, hypotension and tachycardia, bronchial hyperreactivity (cough, ventilatory impairment)</td>
</tr>
<tr>
<td>III</td>
<td>Severe life-threatening multiorgan involvement that requires specific treatment: collapse, tachycardia or bradycardia, cardiac arrhythmias, bronchospasm; the cutaneous signs may be absent or occur only after the arterial blood pressure recovers</td>
</tr>
<tr>
<td>IV</td>
<td>Circulatory or respiratory arrest</td>
</tr>
<tr>
<td>V</td>
<td>Death due to a lack of response to cardiopulmonary resuscitation</td>
</tr>
</tbody>
</table>

Anaphylaxis – Severity

<table>
<thead>
<tr>
<th>Class</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Generalised cutaneous signs: erythema, urticaria with or without angioedema</td>
</tr>
<tr>
<td>II</td>
<td><strong>Moderate multiorgan involvement with cutaneous signs</strong></td>
</tr>
<tr>
<td></td>
<td>Hypotension and tachycardia, bronchial hyperreactivity (cough, ventilatory impairment)</td>
</tr>
<tr>
<td>III</td>
<td>Severe life-threatening multiorgan involvement that requires specific treatment: collapse, tachycardia or bradycardia, cardiac arrhythmias, bronchospasm; the cutaneous signs may be absent or occur only after the arterial blood pressure recovers</td>
</tr>
<tr>
<td>IV</td>
<td>Circulatory or respiratory arrest</td>
</tr>
<tr>
<td>V</td>
<td>Death due to a lack of response to cardiorespiratory resuscitation</td>
</tr>
</tbody>
</table>

### Anaphylaxis – Severity

<table>
<thead>
<tr>
<th>Class</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Generalised cutaneous signs: erythema, urticaria with or without angioedema</td>
</tr>
<tr>
<td>II</td>
<td>Moderate multiorgan involvement with cutaneous signs, hypotension and tachycardia, bronchial hyperreactivity (cough, ventilatory impairment)</td>
</tr>
<tr>
<td>III</td>
<td><strong>Severe life-threatening multiorgan involvement</strong> that requires specific treatment: collapse, tachycardia or bradycardia, cardiac arrhythmias, bronchospasm; the cutaneous signs may be absent or occur only after the arterial blood pressure recovers</td>
</tr>
<tr>
<td>IV</td>
<td>Circulatory or respiratory arrest</td>
</tr>
<tr>
<td>V</td>
<td>Death due to a lack of response to cardiorespiratory resuscitation</td>
</tr>
</tbody>
</table>

### Classification of clinical manifestations of anaphylaxis during anaesthesia. Based on Mertes et al. (6) and Ring and Messmer (86).

<table>
<thead>
<tr>
<th>Class</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Generalised cutaneous signs: erythema, urticaria with or without angioedema</td>
</tr>
<tr>
<td>II</td>
<td>Moderate multiorgan involvement with cutaneous signs, hypotension and tachycardia, bronchial hyperreactivity (cough, ventilatory impairment)</td>
</tr>
<tr>
<td>III</td>
<td>Severe life-threatening multiorgan involvement that requires specific treatment: collapse, tachycardia or bradycardia, cardiac arrhythmias, bronchospasm; the cutaneous signs may be absent or occur only after the arterial blood pressure recovers</td>
</tr>
<tr>
<td>IV</td>
<td>Circulatory or respiratory arrest</td>
</tr>
<tr>
<td>V</td>
<td>Death due to a lack of response to cardiorespiratory resuscitation</td>
</tr>
</tbody>
</table>

### Anaphylaxis – Severity

<table>
<thead>
<tr>
<th>Class</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Generalised cutaneous signs: erythema, urticaria with or without angioedema</td>
</tr>
<tr>
<td>II</td>
<td>Moderate multiorgan involvement with cutaneous signs, hypotension and tachycardia, bronchial hyperreactivity (cough, ventilatory impairment)</td>
</tr>
<tr>
<td>III</td>
<td>Severe life-threatening multiorgan involvement that requires specific treatment: collapse, tachycardia or bradycardia, cardiac arrhythmias, bronchospasm; the cutaneous signs may be absent or occur only after the arterial blood pressure recovers</td>
</tr>
<tr>
<td>IV</td>
<td>Circulatory or respiratory arrest</td>
</tr>
<tr>
<td>V</td>
<td><strong>Death</strong> due to a lack of response to cardiorespiratory resuscitation</td>
</tr>
</tbody>
</table>

Anaphylaxis – Predictors of Severity

1. Rapid onset
   • Often IV and mucous membrane exposure
2. Delayed cutaneous signs
   • Subcutaneous tissue vasoconstriction in response to systemic hypotension
   • May only appear after normalization of BP
3. Bradycardia due to Bezold-Jarisch reflex
   • Cardioinhibitory reflex from the LV
   • Extreme hypovolemia → bradycardia to allow LV to fill
   • Importance of recognition; avoiding atropine

Anaphylaxis – Treatment

- Stop administering drug
- CALL FOR HELP
- A-B-C’s, ACLS if indicated
- *EPINEPHRINE*
- Oxygen, secure airway
- Fluid resuscitation
- Vasopressors
- H1 and H2 blockers
- Corticosteroids
- Patient positioning
- Observation

Anaphylaxis – Definitive Diagnosis

1. Clinical signs and symptoms
2. Elevated tryptase +/- histamine
   - Tryptase more sensitive and specific for anaphylaxis
     - Note: it is a send-out lab
     - Drawn at time of the event and within 1-3hrs of symptom onset; follow until normal (~24hrs later)
3. Skin testing
   - Wait for 4-6 weeks to avoid false negative due to mast cell depletion
   - Prick vs intradermal testing

Outline

I. Case Introduction

II. Anaphylaxis
   I. Definition
   II. Pathophysiology
   III. Diagnosis
   IV. Causal Agents
   V. OR considerations
   VI. Severity
   VII. Treatment

III. Sugammadex
   I. Brief history
   II. Anaphylactic incidence
   III. Cross reactivity

IV. Case Finale

V. Questions
Sugammadex – History

- Designed as the first selective relaxant binding agent
- Modified γ-cyclodextrin; encapsulates aminosteroid NMB drugs in a 1:1 ratio
  - 2.5x more affinity for rocuronium than vecuronium
  - 10x more affinity for rocuronium than pancuronium

Sugammadex – Timeline

• 1990s: Dr. Bom identifies cyclodextrins as potential molecules for selective rocuronium binding
• 1999: First batch of Org 25969 (sugammadex) produced
• 2001: Sugammadex structure and reversal function patented
• 2005: First human studies performed
• 2008: EU approves sugammadex; FDA concerned about bleeding, QT, and anaphylactic risk
• 2010: Japan approves sugammadex
• 2015: December 15th, FDA approves sugammadex

Sugammadex – Anaphylactic Incidence

Figure 1: Comparison of the incidence of anaphylaxis to sugammadex, succinylcholine, and rocuronium.

Sugammadex – Anaphylactic Considerations

- **Dose-dependent response**
  - Higher doses produce more significant reactions

- **Occurs within 5 minutes of administration**

- **Given typically at the end of the case to facilitate emergence**
  - May need to re-establish anesthesia to avoid awareness

- **Sugammadex anaphylaxis often happens without prior exposure**
  - Thought to be due to cross-reactivity

References:


Sugammadex – Cross-reactivity

• We consume 4.1g/person/day of cyclodextrins
• Cyclodextrins are everywhere

HOW AIR FRESHENERS WORK

Some air fresheners just mask bad smells, while others claim to eliminate odors completely. Here, we review the different types of compounds found in air fresheners and how they combat stench.

FRAGRANCES

Air freshener aroma compounds mask bad smells. They include terpenes such as limonene.

ODOR TRAPPING

Cyclodextrins are ring-shaped molecules made from cornstarch. Odor molecules get trapped in their hydrophobic centres.

α-cyclodextrin  β-cyclodextrin  γ-cyclodextrin

© C&EN 2018 Created by Andy Bruning for Chemical & Engineering News

Sugammadex – More Anaphylaxis to Come?

- Reactions are dose-dependent
  - Patient may develop IgE antibodies without significant reactions
  - Big molecule, not readily absorbed via mucus membranes and skin

- West are heavy users of processed foods
  - More likely to have IgE antibodies
  - Counter-argument: frequent mast-cell degranulation from foods in small doses acts to desensitize patients to Sugammadex


Case Finale

• 1140:
  • Staff STAT called
  • 100% oxygen, manual bagging
  • Chest compressions initiated
  • 1mg epinephrine administered
  • Urticarial rash noted on upper chest

• 1142:
  • ROSC, BP 166/78 mmHg, peak pressures <20 cmH₂O

• 1145:
  • Labs drawn, tryptase elevated to 43ng/ml (normal <11.5ng/ml)
Aftermath

- Grade IV anaphylaxis high on our differential
- Diphenhydramine 50mg, famotidine 20mg, and hydrocortisone 100mg given IV; albuterol administered via ETT
- ABG: 7.26/57/210/25.6, Lactate 2.0 → 4.0
- CXR showed RUL opacity consistent with collapse, no pneumothorax or rib fractures
- Intra-op TEE: normal biventricular function, no obvious valvular disease, no pericardial effusion
Aftermath

• Taken to SICU intubated for observation; extubated 2 hours later
  • Tryptase at 1hr still elevated to 21ng/ml; 10hr later 7.2ng/ml
  • Never required epinephrine gtt

• Unremarkable post-op course, discharged POD #5
  • Lost to follow-up, did not complete confirmatory skin testing
Conclusion

• Anaphylaxis is a serious, life-threatening allergic reaction
• Rapid recognition of characteristic signs (rash, bronchospasm, hemodynamic collapse) is important for appropriate management
• OR and GA can mask some of the characteristic signs and symptoms
• The mainstay of therapy: A-B-Cs (ACLS if indicated), epinephrine, fluids
• Many cognitive aids are available
Conclusion

• For definitive diagnosis, obtain tryptase levels at 0, 1, and 24hrs; schedule skin testing 4-6 weeks later
• Sugammadex anaphylaxis can happen without prior exposure
  • Reactions typically occur within 5 minutes of administration
  • Reactions are dose-dependent
  • Consider observing for a few minutes to avoid hemodynamic collapse
Special thanks

Dr. Norah Naughton

Dr. Sathish Kumar
References

References


