Anaphylaxis, Allergy, and Adverse Drug Reactions: Important Considerations for Perioperative Management

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# Disclosures for Jerrold H Levy, MD, FAHA, FCCM

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Objectives

1) Review different adverse drug reactions and life threatening anaphylactic and allergic reactions a clinician may encounter
2) Understand different mechanisms of anaphylaxis and agents often responsible for reactions including drugs, blood products, and environmental agents including latex
3) Discuss therapeutic approaches to treating and preventing anaphylactic reactions and cardiopulmonary dysfunction that occurs
ADVERSE DRUG REACTIONS
PREDICTABLE REACTIONS

• Overdosage or toxicity
• Side effects
• Secondary/Indirect effects
• Drug interactions
UNPREDICTABLE REACTIONS

• Dose-independent
• Not related to drug’s actions
• Related to immune response (allergy)
ANAPHYLAXIS

• Acute inflammatory response
• Inter-relationships with CV system, endothelium, and coagulation
• Mast cell/basophil activation by IgE
• Complement activation by IgG
• Non-immunologic mast cell/complement activation
IgE-mediated release and action of vasoactive amines

Mast cell

Antigen Interaction with at least 2 IgE

Degranulated mast cell

Release of vasoactive amines

Leakage of plasma through endothelial gaps and edema formation

Edema

Smooth muscle contraction

Capillary

Bronchiole

Mucous formation
DIAGNOSING ANAPHYLAXIS: SIGNS AND SYMPTOMS
SYMPTOMS

- Difficulty breathing
- Chest discomfort
- Dizziness, malaise
- Burning, tingling, itching
CARDIOVASCULAR

- Hypotension, cardiac arrest
- Dysrhythmias
- Decreased SVR
- Pulmonary vasoconstriction
MEDIATORS THAT PRODUCE VASODILATION

Prostaglandins: $\text{PGI}_2$, $\text{PGE}_1$, $\text{PGE}_2$, $\text{PGD}_2$

Histamine: ($\text{H}_1$ and $\text{H}_2$ effects)

Kinins: bradykinin, kallikrein

Leukotrienes

Nitric oxide

Platelet-activating factor, Substance P
VASCULAR ENDOTHELIUM

Angioedema

• Well demarcated non-pitting edema caused by pathological factors that cause urticaria
• Reaction occurs deeper in dermis and subcutaneously
• Face, tongue, lips, eyelids most commonly affected
• May cause respiratory distress if larynx involved
RESPIRATORY

• Bronchospasm/wheezing
• Airway edema
• High airway pressures
• Acute pulmonary edema
Asthma: Pathological changes

NORMAL AIRWAY

AIRWAY DURING AN ASTHMA ATTACK

- Mucus
- Submucosa
- Airway
- Mucosa
- Muscle
- Mucus-producing gland
- Swollen submucosa
- Airway narrows
- Excess mucus
- Secretion of mucus from gland increases
Asthma and Airway Inflammation

CLINICAL FINDINGS

• Bronchospasm was most difficult feature to treat
• 3/4 deaths occurred in these patients
• Postmortem showed acute emphysema and pulmonary edema
CAUSES OF WHEEZING

- Reactive airways
- Pulmonary edema
- Pneumothorax
- Anaphylaxis
- Aspiration
CAUSES OF WHEEZING

• Endobronchial intubation
• Airway obstruction
• ETT obstruction
• Pulmonary emboli
CLINICAL SIGNS

- Circulatory collapse 68%
- Cardiac arrest 11%
- Bronchospasm 23%
- Widespread flush 55%
- Edema 26%
DIFFERENTIAL DIAGNOSIS OF ANAPHYLAXIS

• Administration of sedative, hypnotic, or anesthetic drugs
• Asthma/bronchospasm
• Cardiogenic shock
• Disconnection or overdosage of vasoactive drug infusions
• Dysrhythmias
• Tension pneumothorax
DIFFERENTIAL DIAGNOSIS OF ANAPHYLAXIS

• Pericardial tamponade
• Postextubation stridor
• Pulmonary edema
• Pulmonary embolus
• Septic shock/SIRS
• Vasovagal reactions
• Venous air embolism
MECHANISMS OF ANAPHYLAXIS

• Mast cell/basophil activation by IgE
• Complement activation by IgG and direct activation
• Non-immunologic inflammatory activation
**GRANULOCYTES**

- Complement Activation
- Leukoagglutinins

**AGGREGATION**

**PULMONARY LEUKOSTASIS**

- Prostaglandins
- Leukotrienes
- Lysosomal Enzymes
- $O_2$ Free Radicals

**ENDOTHELIAL DAMAGE**

- INCREASED PERMEABILITY
- PULMONARY HYPERTENSION

DRUGS THAT RELEASE HISTAMINE

- Antibiotics: vancomycin
- Hyperosmotic agents
- Muscle relaxants
- Opioids
- Polybasic compounds
- Thiobarbiturates
Agents most often implicated in perioperative anaphylaxis

- Antibiotics
- Blood products
- Muscle relaxants
- Proteins (aprotinin, latex and protamine)
NMBAs and Allergy

- Complete antigens
- Some are mirror molecules
- Potential histamine release
- Potential for false positive skin tests
How to make a muscle relaxant

- Take 2 bisquaterternary ammonium ions, and separate 10-11 nm (Å) with 8-10 molecules
- Linear molecule is depolarizing (decamethonium, succinylcholine)
- Add bulky side groups (benzyl-isoquinolines) or insert into steroidal ring
STEROID MUSCLE RELAXANTS: Molecular Structure

Vecuronium
NMBAs

- Benzylisoquinolines
- Amino steroids
- Acetylcholine homologues

• French reports use undiluted drug in prick testing; ROC, VEC are 10 and 1 mg/mL.
• Dhonneur showed if French prick test validity were applied, all reacting volunteers would have fulfilled criteria of allergy. (Moneret-Vautrin DA:Allerg Immunol (Paris) 2002; 34:233) and (Rev Fr Allergol 1997;42:776).
LATEX ALLERGY

Preoperative considerations:
• Allergy to bananas, avocados, kiwis, mangos, stone fruits
• Chronic care (latex-based products)
• Spina bifida with multiple ops
• Intraop anaphylaxis: ?etiology
• Repeated surgical procedures (>9)
• Intolerance to latex-based products
• Healthcare workers
Guidelines for managing potential drug reexposures:

3) Initial (test) doses may produce anaphylaxis, thus clinicians must be cautious during a re-exposure. Test doses should be administered intravenously at least 10 min before the loading dose.

THERAPY (1)

- Stop antigen
- Maintain airway / 100% O₂
- Discontinue anesthetic agents
- Volume expansion
- Epinephrine
THERAPY (2)

• Catecholamines/AVP
• Antihistamines
• Bronchodilators
• Corticosteroids
• Bicarbonate
• Airway evaluation
THERAPY(3)

• If hypotension persists, consider Vasopressin
• Echo: TEE/TTE
• RV failure?
• 12-24 hour ICU/PACU observation
• Steroid coverage
ARGININE VASOPRESSIN

- Peptide from the posterior pituitary
- $V_1$-receptor: pressor response
- $V_2$-receptor: ADH effect
- During CPR, plasma AVP levels higher in ROSC pts
- IIb recommendation in ACLS 2000
VASOPRESSIN

• Inhibits product of cGMP by IL-1 and ANP
• Inhibits ATP-activated potassium channels of VSM
• Counteracts pathologically activated vasodilation
VASOPRESSIN

THERAPY(4): RV FAILURE

- Reassess ventilation: I/E ratios?
- Treat bronchospasm
- Phosphodiesterase inhibitors
- Vasodilators: NO, PGE$_1$, PGI$_2$
- LA norepinephrine
- Mechanical support: IABP, VAD, CPB
SUMMARY

• Understanding the spectrum of ADRs and anaphylaxis is important when evaluating potential reactions.

• If you have a reaction, draw blood for Tryptase-within 1-2 hrs, then 24 hrs later
SUMMARY

• Skin testing with NMBAs and opioids need to be performed with appropriate dilutions to avoid false positive responses.

• Rapid diagnosis, and aggressive therapy is important to avoid a disastrous outcome.