Epinephrine Auto-Injectors & Trends in Oral Immunotherapy

Erika Gonzalez-Reyes, MD
Chief of Allergy, Immunology & Rheumatology
Associate Professor of Clinical Pediatrics
Baylor College of Medicine
Children’s Hospital of San Antonio
Anaphylaxis

- Acute systemic reaction allergic reaction that varies in severity from mild to life-threatening reaction
- Can progress rapidly
- Previous reactions do not predict severity of future reactions
Symptoms of Anaphylaxis

Airway
- 70% of episodes
  - Larynx: pruritus and tightness in throat, dysphonia, and hoarseness
  - Lung: dyspnea, chest tightness, wheezing/bronchospasm

Skin
- 80%–90% of episodes
  - Urticaria, pruritus, flushing
  - Mucosal tissue: pruritus and swelling of lips, tongue, uvula/palate

Central nervous system
- Up to 15% of episodes
  - Uneasiness, throbbing headache, dizziness, confusion, tunnel vision

Cardiovascular system
- Up to 45% of episodes
  - Chest pain, hypotension, tachycardia, weak pulse, faintness

Gastrointestinal tract
- Up to 45% of episodes
  - Nausea, cramping, abdominal pain, vomiting, diarrhea

---

a Potentially life-threatening symptoms.
## Anaphylaxis Location

<table>
<thead>
<tr>
<th>Location of Reaction</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home</td>
<td>51%</td>
</tr>
<tr>
<td>Hospital/clinic</td>
<td>14%</td>
</tr>
<tr>
<td>Family/friend’s home</td>
<td>7.3%</td>
</tr>
<tr>
<td>Work</td>
<td>6.1%</td>
</tr>
<tr>
<td>Restaurant</td>
<td>6.1%</td>
</tr>
<tr>
<td>Traveling</td>
<td>4.6%</td>
</tr>
<tr>
<td>School</td>
<td>3.4%</td>
</tr>
<tr>
<td>Outdoors</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

DID YOU KNOW?

40% of children with food allergies have experienced a severe or life-threatening reaction.

125,000 ER visits per year

Reactions can range from a mild response to **anaphylaxis**, a severe and potentially deadly reaction.

Every 3 minutes a food allergy reaction sends someone to the **ER**.

As many as **1500 deaths**
Treatment of Anaphylaxis

EPINEPHRINE
## Anaphylaxis in the Community Survey (N=1385)

**Reasons Epinephrine Auto-Injectors Were Not Used to Treat Anaphylaxis**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamine was used</td>
<td>38%</td>
</tr>
<tr>
<td>Did not receive a prescription for epinephrine auto-injector</td>
<td>28%</td>
</tr>
<tr>
<td>Allergic reaction was mild</td>
<td>13%</td>
</tr>
<tr>
<td>Asthma puffer used</td>
<td>8%</td>
</tr>
<tr>
<td>Did not have an epinephrine auto-injector available</td>
<td>8%</td>
</tr>
<tr>
<td>Unsure when to give injection</td>
<td>8%</td>
</tr>
<tr>
<td>In previous reaction no treatment was needed</td>
<td>8%</td>
</tr>
<tr>
<td>Afraid to inject epinephrine</td>
<td>6%</td>
</tr>
</tbody>
</table>

In a separate survey—Anaphylaxis in America—28% of responders with confirmed anaphylaxis only self-administered an antihistamine to treat their signs and symptoms.

---

Risk Factors for Fatal Anaphylaxis

• Underused - failure to treat with epinephrine
• Delayed treatment with epinephrine
• Improper administration
  • Inappropriate route of administration
• Rapid progressions of symptoms

Commercially available epinephrine

- Several epinephrine auto-injectors are currently available
- All contain the drug epinephrine
- Each device has its own unique set of instructions for administration
- Understanding the difference is important in maximizing successful administration
Commercially available epinephrine

- The FDA has assigned a BX rating to all EAI’s
- Despite BX rating, EAIs can be substituted in 21 states
- HCP and patients should be made aware of the differences among EAIs
- Recognize the negative impact substitution and inadequate education may have on adherence and proper usage during an anaphylactic event.
WHAT EPINEPHRINE PRODUCTS ARE CURRENTLY AVAILABLE?
<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Available Strengths</strong></td>
<td>0.3 mg, 0.15 mg 1:1000</td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Amedra Pharm</td>
</tr>
<tr>
<td><strong>Generic Available</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Include Trainer</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Talking Feature</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Needle exposed after injection</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Discount Program</strong></td>
<td>Copay card provides up to $100 discount per twin pack (can be redeemed up to 3 times)</td>
</tr>
<tr>
<td><strong>Refill Reminder Feature</strong></td>
<td>No</td>
</tr>
<tr>
<td>Feature</td>
<td>Details</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Available Strengths</strong></td>
<td>0.3 mg, 0.15 mg 1:1000</td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Sanofi-Aventis U.S.</td>
</tr>
<tr>
<td><strong>Generic Available</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Include Trainer</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Talking Feature</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Needle exposed after injection</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Discount Program</strong></td>
<td>Copay card provides up to $100 discount per twin pack (up to 3 per prescription)</td>
</tr>
<tr>
<td><strong>Refill Reminder Feature</strong></td>
<td>E-mail &amp; App</td>
</tr>
<tr>
<td><strong>Available Strengths</strong></td>
<td>0.3 mg, 0.15 mg 1:1000</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Mylan, Inc</td>
</tr>
<tr>
<td><strong>Generic Available</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Include Trainer</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Talking Feature</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Needle exposed after injection</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Discount Program</strong></td>
<td>Copay card provides up to $100 discount per twin pack</td>
</tr>
<tr>
<td><strong>Refill Reminder Feature</strong></td>
<td>E-mail</td>
</tr>
</tbody>
</table>
### Epinephrine Injection, USP auto-injector, AG Adrenaclick

<table>
<thead>
<tr>
<th>Available Strengths</th>
<th>0.3 mg, 0.15 mg 1:1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Lineage Therapeutics</td>
</tr>
<tr>
<td>Generic Available</td>
<td>**</td>
</tr>
<tr>
<td>Include Trainer</td>
<td>No</td>
</tr>
<tr>
<td>Talking Feature</td>
<td>No</td>
</tr>
<tr>
<td>Needle exposed after injection</td>
<td>Yes</td>
</tr>
<tr>
<td>Discount Program</td>
<td>Copay card provides up to $100 discount per twin pack (can be redeemed up to 3 times)</td>
</tr>
<tr>
<td>Refill Reminder Feature</td>
<td>E-mail</td>
</tr>
</tbody>
</table>
Epinephrine PFS

- Adamis Pharmaceuticals
- Company filed a New Drug Application with the FDA (May 2014)
- If approved the PFS intends to compete as a low-cost epinephrine therapeutic alternative
- Would come in 0.3 mg (1:1000) prefilled syringe
Another EIA in the works?

- Potential approval of an AB rated generic EpiPen
- Estimated to be launched in early 2016
- TEVA pharmaceuticals
Dosing

- Recommendations are based on anecdotal experience
- Vary
  - Maximum initial dose
  - Route of injection (SC vs IM)
  - Interval (5-30 mins)
- Evidence is derived from clinical pharmacology studies and population based studies
- 0.01mg/kg
### Dosing and Administration

<table>
<thead>
<tr>
<th>Epinephrine Concentration</th>
<th>Patient Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg (0.3 mL, 1:1000)</td>
<td>≥30 kg (≥66 lb)</td>
</tr>
<tr>
<td>0.15 mg (0.3 mL, 1:2000)</td>
<td>15-30 kg (33-66 lb)</td>
</tr>
</tbody>
</table>
Dosing

- Too little epi is better than NO epi
- Too much epi is better than NO epi
- Expired epi is better than NO epi
- In an emergency situation... Give what you have
Oral Immunotherapy Trends
### Tolerance

- Protective effect depends on daily uninterrupted ingestion of food allergen
- Protective effect may be lost if dose is interrupted

### Desensitization

- Permanent tolerance that allows food to be ingested without allergy symptoms despite periods of abstinence
Oral Immunotherapy

- OIT is still considered experimental
- Goal is to alter the allergic response to food allergen so that the patient
  - Desensitized
  - Tolerant
- Before these approaches can be applied in clinical practice they must be carefully evaluated for side effects
  - Acute adverse reactions
  - Long term side effects
    - Toxicity
    - Overstimulation of the immune system
Oral Immunotherapy

- Generating increased interest
- Studies have shown a high rate of desensitization
- Fewer patients become tolerant
- The rate of acquisition of tolerance is higher than that seen in patients who completely avoid the allergen
Oral Immunotherapy

- Protocols have most clearly been reported
  - Milk, egg, peanut
- Patients are generally started on a very small daily dose
- Slowly advance to maintenance dose
- Alternative is to combine OIT with administration of anti-IgE antibodies
- Introduction of extensively heated milk & egg is an alternative approach
Milk OIT

- Likelihood of developing full tolerance was 10 fold higher and partial tolerance was 5 fold higher when compared to children on milk elimination diet
- Risk of adverse reaction was 34-fold higher
  - Lip/mouth pruritis
  - Approximately 10% needed epinephrine
- Limited long term follow-up
- Some data suggest that desensitization may not be maintained in some patients
- Additional long term follow-up is needed to determine the ideal patient
Egg OIT

- Appears to be effective in desensitizing most patients
- Permanent tolerance is induced less frequently
- Protocols were done using egg-white powder
- Mild allergic symptoms were common, particularly in the first 10 months of dosing
Peanut OIT

- Peanut allergy is rarely outgrown
- Uncontrolled studies have shown that OIT can lead to successful desensitization in patients who are able to tolerate therapy
- Smaller percentage of patients have sustained unresponsiveness after discontinuing OIT
- Higher rates of side effects when compared to milk and egg OIT
- More significant improvement in QOL scores
Things to consider

- Allergic reactions during home dosing is common
- Patients required treatment, including, epinephrine during home dosing phase
- At least one case of life-threatening anaphylaxis has been reported during the escalation phase of OIT
- 10-20% incidence of EGID or eosinophilic esophagitis have been reported in patients undergoing OIT
Things to consider

- OIT can lead to desensitization but tolerance is more difficult to achieve
  - Would longer OIT therapy help?
  - Would adding adjuvants help?
- Oral Immunotherapy to multiple foods
- OIT combined with anti-IgE
LEAP Study

- Learning Early About Peanut Allergy Study
- Published in the NEJM March 2015
- Looked at 640 high risk United Kingdom Infants
- Between 4 to 11 months of age
- Randomized
  - consume peanut products at least 3 times a week
  - Avoidance diets
- Negative skin test to peanut or SPT wheal diameters between 1 & 4 mm
LEAP Study

- Demonstrated an 80% relative risk reduction in high risk infants if peanut was introduced between 4 & 11 months of age
- AAP endorsed the guidance of early peanut introduction (June 2015)
- The practice of early introduction is safe and effective in selected high risk infants
- No data investigating the benefit or risk or early peanut introduction in the general to low-risk populations
- More extensive guidelines are upcoming
The Viaskin® Peanut allergy patch

- Recently received FDA “Fast Track” designation following encouraging safety test results.
- If FDA approved following additional testing it will be the first skin patch intended to treat peanut allergies.
- Designed for Epicutaneous Immunotherapy (EPIT) of patients with peanut allergies.
- Administers allergens through the skin in order to improve the patient's tolerance of peanuts.
- The next step is a clinical study to demonstrate the safety and effectiveness of the peanut patch.
- If the product is able to desensitize peanut-allergic patients, it may receive FDA approval, becoming available to U.S. patients with peanut allergies.
Questions?