therapeutics letter
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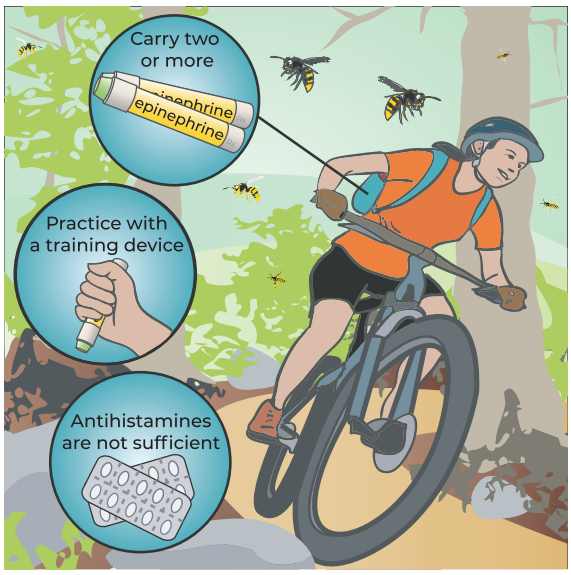
THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Epinephrine autoinjectors available in Canada



Anaphylaxis is one of the most dramatic health crises. Experiencing or witnessing this acute and serious allergy event is a powerful incentive to learn more, yet many health care professionals must act without the benefit of personal experience. The Canadian Institute for Health Information estimates that anaphylaxis makes up 8% of the approximately 171,000 annual emergency department visits for allergy in Canada.[1]

Signs and symptoms of anaphylaxis range in severity and may include:[2]

- **Cutaneous:** goose bumps, itching, flushing, morbilliform rash, hives, angioedema.
- **Respiratory:** rhinitis, throat itching/tightness, dyspnea, wheeze, upper airway obstruction, respiratory arrest.
- **Gastrointestinal:** nausea, vomiting, diarrhea, abdominal cramping.
- **Cardiovascular:** hypotension, syncope, diaphoresis, chest pain, shock, dysrhythmia, cardiac arrest.
- **Neurologic:** feeling of impending doom, anxiety, irritability, confusion, loss of consciousness, seizures.
- **Other:** uterine cramping, metallic taste in mouth.

Self-injectable epinephrine (adrenaline) is recommended for people with a history of anaphylaxis:[2,3,4]

a) when there is a high probability of recurrence;

b) when allergen avoidance is not always possible (e.g. foods, stinging insects, environmental triggers, exercise);

c) when the allergen has not been identified (idiopathic anaphylaxis).

Epinephrine is a non-selective (alpha and beta) adrenergic receptor agonist administered to counter the systemic vasodilation that occurs during anaphylaxis.[5,6] It increases peripheral vascular resistance, increases cardiac contractility and heart rate, decreases mucosal edema and induces bronchodilation.[5,6]

What evidence underlies the use of epinephrine autoinjectors?

Epinephrine was first marketed almost 120 years ago, yet many practical issues are not firmly answered. Should epinephrine be administered at the earliest onset of mild symptoms or reserved for severe symptoms? What is the optimal dose? A Cochrane 2008 systematic review identified ethical and practical issues associated with performing randomized, double-blind, placebo-controlled trials of epinephrine during anaphylaxis.[7] A 2015 American anaphylaxis guideline notes transparently that the "**treatment of anaphylaxis is, at best, based on indirect and observational studies and primarily on consensus**."[2] In the absence of a clear definition of evidence-based use, viewpoints diverge as to whether epinephrine autoinjectors are underused or overused.[8-11]

What advice can healthcare providers offer patients about epinephrine autoinjectors?

- Injectable epinephrine is the first-line intervention for anaphylaxis.[2,3,4,6]
- Subsequent reactions may be more or less severe, or follow the same clinical course therefore the decision when exactly to administer epinephrine will necessarily involve some judgement. American and Canadian guidelines however recommend the administration of epinephrine promptly at the onset of anaphylaxis.[2,3,4]

Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Anesthesiology, Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: 604 822 0700
Fax: 604 822 0701
E-mail: info@ti.ubc.ca
www.ti.ubc.ca

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- **Oral medications do not work quickly enough** for rapidly evolving, severe systemic allergic reactions.[2,3] Do not expect them to be effective for upper airway obstruction, hypotension, or cardiorespiratory arrest.[2,3]
  - These include H_1-antihistamines (e.g. diphenhydramine), H_2-antihistamines (e.g. ranitidine), corticosteroids (e.g. prednisone, dexamethasone). Liquids, liquid-gel capsules and dissolvable tablet formulations of antihistamines are not effective solutions to this problem.
- Epinephrine autoinjectors are designed to be injected into the middle, outer thigh and held in place for several seconds.[5,12]
  - **Watching demonstration videos** and **practicing with a training device** is recommended to increase confidence with autoinjector technique.
- For people at risk for anaphylaxis having **access to at least two epinephrine autoinjectors** is recommended for several reasons:[2,3]
  - Each device delivers a single fixed-dose of epinephrine.[5,12]
  - Anaphylaxis may occur far from emergency medical care and a repeated dose in 5 to 15 minutes may be necessary.[5,12]
  - Epinephrine has a short half-life and the optimal dose is unclear.[2]
  - Autoinjectors have in some cases failed to deploy correctly or have been injected accidentally into a finger or thumb.[13,14,15]
- Contacting emergency medical services after the administration of epinephrine is advised in the event of a biphasic (second) or prolonged reaction.[2,3,4,5,12]

Using an ampule or multidose vial of epinephrine and a syringe is less expensive. The 2015 American guideline raised concerns associated with using an ampule or multidose vial, citing the potential for a delay in administration or inaccurate dosing.[2] In response to the 2018 EpiPen shortage, the College of Pharmacists of British Columbia and the BC Pharmacy Association developed tools for dispensing and counselling on the use of epinephrine ampules or vials with syringes: http://bcpharmacists.org/news/epipen_shortage

Epinephrine autoinjectors available in Canada

Brand Name	Dose per injector	Wholesaler cost per injector[17]
EpiPen Jr	0.15 mg	$95
EpiPen	0.30 mg	$95

- 0.15 mg dose: children who weigh between 15 and 30 kg[5]
- 0.30 mg dose: children who weigh ≥ 30 kg and adults[5]
- Canadian Society for Allergy and Clinical Immunology position statement on epinephrine autoinjector dose for children who weigh less than 15 kg[16] can be accessed here: https://doi.org/10.1186/s13223-015-0086-9
- AUVI-Q epinephrine autoinjector: made temporarily available by Health Canada as a consequence of the 2018 EpiPen® shortage (AUVI-Q wholesaler cost: $183 per injector)[12,17,18]
- A generic epinephrine autoinjector (Taroclick Epinephrine) was approved by Health Canada in 2018 but is not currently marketed[19]

Conclusions

- People at risk for anaphylaxis in the outpatient setting should be advised to have **access to at least two epinephrine autoinjectors** especially when they are far from emergency medical care (home, travel, occupation, recreational activities).
- **Oral medications such as antihistamines and corticosteroids are inadequate to treat rapidly-evolving, severe allergic reactions.**
- Healthcare providers, especially community pharmacists, can access placebo demonstration epinephrine autoinjectors (trainers) to be used in patient teaching.

Links to watch demonstration videos and access placebo training devices:
https://ti.ubc.ca/epipen-videos
https://ti.ubc.ca/epipen-starter-kit

For the complete list of references go to: **https://ti.ubc.ca/letter119**

The draft of this Therapeutics Letter was submitted for review to 130 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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