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Epinephrine Auto-Injectors

Ozlem Yılmaz Ozbek*

Baskent University, Faculty of Medicine, Ankara, Turkey

***Corresponding author:** *Ozlem Yılmaz Ozbek, Assoc. Prof. of Pediatric Allergy, Baskent University, Faculty of Medicine, 6. Cadde, No: 70/1, 06490, Bahcelievler, Ankara, Turkey, Tel: +90 312 2152114; Fax: +90 312 2157595; E-mail: ozlemyozbek@gmail.com*

Abstract

Anaphylaxis is a systemic, life-threatening reaction and immediate treatment is essential. The reaction can be fatal even with epinephrine injection. Epinephrine auto-injectors have been used in the emergency treatment of anaphylaxis since the 1980s. In this review, indications for the prescription, types, administration, and the problems with the use of epinephrine auto-injectors are discussed. The importance of patient and caregiver education is highlighted.

Keywords

Anaphylaxis, Epinephrine, Epinephrine Auto-Injector, Treatment

Introduction

Anaphylaxis is a systemic, potentially life-threatening allergic reaction that frequently involves severe respiratory symptoms and cardiovascular collapse [1]. Prompt injection of intramuscular epinephrine is essential. Without epinephrine injection, fatal outcomes can be more frequent; indeed, delayed administration of epinephrine has also been associated with increased mortality [2]. Epinephrine auto-injectors (EAIs) have been the corner stone in the emergency treatment of anaphylaxis since the 1980s [3]. Other drugs, such as antihistamines, corticosteroids or beta-agonists may be helpful, but should not be administered instead of epinephrine. Since anaphylaxis usually takes place remote from medical aid, people who are at risk of anaphylaxis should be educated about emergency treatment. An EAI should be prescribed and the patient should be informed how and when to properly use it [1, 4-6].

Indications for the prescription of EAI

In order to prescribe EAIs, at least one of these absolute indications should be present [7-10]:

1. Previous anaphylaxis triggered by food, latex or aeroallergens
2. Previous exercise-induced anaphylaxis
3. Previous idiopathic anaphylaxis
4. Concomitant unstable or moderate to severe-persistent asthma and a food allergy (apart from oral allergy syndrome)
5. Venom allergy in adults with previous reactions (not receiving maintenance venom immunotherapy) and children with more than cutaneous/mucosal systemic reactions
6. Mast cell disorders or increased baseline serum tryptase concentrations in addition to any previous systemic allergic reaction to insect stings, even in venom immunotherapy treated patients

Prescribing at least one EAI with any of the following additional factors should be considered [11-12]:

1. Previous mild-to-moderate allergic reaction to peanut and/or tree nut
2. Teenager or young adult with a food allergy
3. Remote from medical help and previous mild to moderate allergic reaction to a food, venom, latex or aeroallergens
4. Previous mild-to-moderate allergic reaction to traces of food

According to current guidelines, the weight-based dose of epinephrine (1:1000; 1 mg/ml) is the same in children and adults (0.01mg/kg). When using an EAI, children weighing 15-30 kg should receive a 0.15 mg dose and children over 30 kg or adults should be given 0.3 mg [13]. Consistent with the patient's clinical status, such as incomplete resolution or recurrence of symptoms of anaphylaxis, further doses may be administered in every 5–15 minutes, or more frequently if needed [1,4-6]. Current data reveal that approximately 10–20% of anaphylaxis patients need repeated epinephrine injections due to biphasic reactions or inadequate treatment response to the initial dose. [14]. Therefore, it is recommended that all patients at risk for anaphylaxis always carry two epinephrine doses [6].

Types of EAIs

Commercially, there are 6 different EAIs (Table 1). Among these, Epipen (Mylan Specialty L.P, USA) was the first licensed and commonly used EAI since 1987. EpiPen is a single use, cartridge-based epinephrine auto-injector. The device was released in the European Union (EU) in 1994 and is available in two forms; EpiPen and EpiPen Junior, which contain 0.3 mg and 0.15 mg of epinephrine, respectively. Recently, another commercial form of Epipen that contains double auto-injectors in one pack has been launched (Epipen 2-pak, Mylan Specialty L.P, USA). Another EAI, AnaPen (Lincoln Medical, UK) based on the subcutaneous insulin

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Table 1: Features of some epinephrine auto-injectors

	Epipen	Jext	Auvi-Q/ Allerject	Emerade
Available doses (mg)	0.15/0.3	0.15/0.3	0.15/ 0.3	0.15/ 0.3/ 0.5
Availability	Worldwide	Europe	USA/Canada	Europe
Exposed needle length (cm)	1.3/1.50	1.53	1.27/1.57	1.6/2.5/2.5
Shelf-life (months)	12-18	24	12-18	30
Needle protection	yes	yes	yes	Yes
Injection time (seconds)	10	10	5	5
Special features	1or 2-Pak		Audio cues	Needle length

pen Autoject Mini, is a single use, syringe-based delivery system. Three forms of this product are available, named AnaPen 500, AnaPen 300 and AnaPen 150; which contain 0.5, 0.3 and 0.15 mg of epinephrine, respectively. A different EAI form that contained two individual doses in case of a need for repeated application was previously sold under the trade name Twinject. However, Anapen 500 and Twinject are no longer available.

A new EAI, Jext (ALK-Abello Ltd, UK) approved by European regulators in 2010 was launched in the EU. Another version of EAI, Auvi-Q (Sanofi Company, US) has been approved by the U.S. Food and Drug Administration (FDA) in 2012. This form is rectangular in shape (3.5x2x0.5 inches) and contains a sound chip in it to provide auditory signals to the patient or caregiver to help in the precise use of the instrument. The same device has been launched in Canada by the same company under the trade name Allerject (Sanofi Company, Canada). In 2013, the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) approved Emerade (Namtall AB, UK), the first auto-injector which contains 300µg or 500µg epinephrine with a 25mm length needle. Emerade auto-injector is available also in 150 µg (needle length 16mm).

Administration of EAIs

With regard to the mode of administration, it has been recommended by current guidelines that epinephrine be given preferentially via intramuscular route in the mid anterolateral aspect of the thigh [5,6,8]. Accordingly, all current EAIs are universally recommended to be injected in this anatomical location. This recommendation is based on observational studies in children and adults that demonstrate that this way permits optimal absorption. However, studies using imaging modalities have found that the length of the EAI needle is sometimes not long enough to reach muscular tissue in the thighs of obese individuals [15]. Whether this is clinically relevant has yet to be proven, but it is hypothesized that this may affect the absorption given the vasoconstrictive properties of epinephrine when given through subcutaneous tissues. Therefore, as mentioned above, UK-MHRA approved Emerade.

Epinephrine is light sensitive and should be stored in the carrier tube provided to protect it from light. Storage at 20° to 25°C (68° to 77°F) is recommended, but deviations between 15-30°C (59° to 86°F) is permitted. Not to refrigerate is advised. Before using, checking to make sure the solution in the auto-injector is clear and colorless is suggested. If the solution is discolored (pinkish or brown color), cloudy, or contains particles, the EAI should be replaced.

In order to use, EAIs should be removed from the carrier tube, and then the safety release should be detached by pulling the injector straight up without bending or twisting. Afterwards, the EAI should be held the with needle tip near the middle of the outer thigh (upper leg). Swinging and firmly pushing the needle tip against the middle of the outer thigh until it 'clicks', then keeping the auto-injector firmly pushed against the thigh at a 90° angle (perpendicular) to the thigh are the next steps. The injector should be held firmly against the thigh for approximately 10 seconds to deliver the medicine.

Problems with the use of EAIs

Common mistakes in use of EAIs arise at the same stages of application. The most frequent mistake (48-57%) made by physicians during intramuscular application of EAIs is failing to hold the injector against the thigh for the full 10 seconds that is necessary for injection of a sufficient amount of drug. The second mistake (20-50%) in the use of EAIs is application of the injector without proper pressure to the thigh [16-17]. These mistakes can result in administration of an insufficient amount of epinephrine. Unintentional injections from epinephrine auto-injectors have been reported in the medical literature (10-16%) [18].

Side effects and contraindications for use of EAIs

The most common side effects that can happen within minutes of epinephrine injection include anxiety, pallor, increased heart rate, headache or dizziness. Intramuscular epinephrine administration has a lower rate of cardiovascular complications compared to intravenous [19]. In general, when epinephrine is given appropriately, serious adverse effects are not a concern in otherwise healthy children and adolescents. However, the benefits of administration of epinephrine in adult anaphylaxis patients with or at risk of coronary artery disease must be determined carefully because of its cardiac effects [3]. There are no absolute contraindications to the administration of epinephrine for anaphylaxis in any patient [5].

Conclusion

Due to the unpredictable nature of anaphylaxis patients should be prescribed intramuscular EAIs and carry these with them at all times. Patients also need to be able to use their auto-injectors correctly while under high stress, when an anaphylactic reaction occurs. Despite this, an alarming number of patients fail to carry their auto-injectors and many patients and healthcare professionals do not know how to use the device correctly, despite having had training [17,20]. Over time, patients tend to not carry EAI or use the drug too late [17,21]. Therefore, the education should be repeated periodically. Several investigations showed that education of patient or caregiver is utmost important [17,20-22]. The importance of the proper use of EAIs should be taught to the patients.

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