



An update on self-injectable epinephrine

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Purpose of review

Epinephrine is an important life-saving treatment in patients with anaphylaxis. However, despite the guidelines recommending the use of epinephrine in the management of all patients with anaphylaxis, many patients are either not prescribed epinephrine auto-injectors (EAI) or remain hesitant to use them.

Recent findings

In this review, we examine our current knowledge base regarding EAI, including issues related to dosing, medication availability and new modes of administration. Our findings suggest that all patients at risk for anaphylaxis should always carry two epinephrine doses. Once an EAI is prescribed, the patient should receive appropriate education on when and how to use it and it should be administered without delay. Current EAI devices have been redesigned to address limitations and decrease unintentional injury.

Summary

Epinephrine remains the cornerstone of anaphylaxis treatment and EAI are critical because of their ability to rapidly deliver this potentially life-saving medication outside of a medical setting. Continued efforts are needed to establish evidence-based parameters for delivery of this medication and to optimize education of healthcare providers and patients on the use of EAI.

Keywords

anaphylaxis, auto-injector, epinephrine, food allergy, stinging insect allergy

INTRODUCTION

Epinephrine is the first-line treatment of anaphylaxis, a potentially life-threatening medical emergency. Introduced in the 1980s, epinephrine auto-injectors (EAI) are the cornerstone of first-aid management of anaphylaxis in the community [1]. Because delays in therapy have been associated with fatalities [2,3], it is recommended by all current guidelines [4,5^{*},6,7] that EAI be available at all times to patients at risk for anaphylaxis and be administered without delay in the setting of anaphylaxis. Furthermore, additional doses may be administered every 5–15 min based on the patient's clinical status. Other medications such as antihistamines, corticosteroids and beta-agonists represent adjunctive therapies, but should not be given in the place of epinephrine. In this review, we examine our current knowledge base regarding EAI, including issues related to dosing, medication availability and new modes of administration.

PHARMACOLOGY OF EPINEPHRINE

Epinephrine is a direct-acting sympathomimetic agent with both alpha-adrenergic and beta-adrenergic properties. These properties result in effects on

many target organs, including the heart/cardiovascular system (increased vasoconstriction and increased ionotropy/chronotropy), skin and mucosal surfaces (decreased edema) and the lungs (bronchodilation). Epinephrine also downregulates further mast cell release of the mediators of inflammation including tryptase and histamine. Therefore, epinephrine has the unique ability to rapidly address the multiorgan system manifestations of anaphylaxis.

Epinephrine dosing

Randomized, double-blind, placebo-controlled trials on the use of epinephrine in anaphylaxis

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KEY POINTS

- Epinephrine auto-injectors remain the cornerstone of treatment of anaphylaxis in the community setting.
- All patients at risk for anaphylaxis should be prescribed two epinephrine auto-injectors and be thoroughly educated on how and when to use them.
- Deficiencies remain in evidence-based guidelines on the appropriate dosage and mode of administration of epinephrine for anaphylaxis.
- Further research is needed on how to improve education of patients on the use of epinephrine auto-injectors.
- Currently available epinephrine auto-injector devices have been redesigned to address limitations and decrease unintentional injury.

would be unethical to perform because of our collective knowledge on the life-saving properties of this medication [8[¶]]. Therefore, much of what we know in terms of its optimal dosing and mode of administration comes from clinical experience, observational studies (including fatality studies) [2,3] and a limited number of prospective studies [9–11]. All current guidelines recommend that epinephrine (1:1000; 1 mg/ml) be given at the dose of 0.01 mg/kg in children with a maximum dose of 0.3 mg. In adults, the standard dose is 0.3 mg with a maximum dose of 0.5 mg. Additional doses may be administered every 5–15 min based on the patient's clinical status because of incomplete resolution or recurrence of symptoms of anaphylaxis [4,5[¶],6,7].

In the United States, EAs are exclusively available in two fixed doses (0.15 and 0.30 mg). It is generally recommended that all adults and children weighing at least 25 kg be prescribed the 0.30 mg auto-injector regardless of their weight or body habitus [7]. In Europe, a 0.5-mg auto-injector is also available and is recommended for those weighing at least 60 kg. Meanwhile, children weighing less than 25 kg are most often prescribed the 0.15 mg auto-injector [7]. Many times, this results in children receiving what we would consider to be less or more than optimal dosing of epinephrine [12]. For example, infants weighing significantly less than 15 kg are prescribed the 0.15 mg dose because the alternative of providing a syringe, ampule and needle is considered less than ideal. However, data to guide the correct dosages in both adults and children are lacking and further studies are required to make evidence-based recommendations in this regard.

Multiple doses

Currently available data indicate that 10–20% of anaphylaxis patients will require repeated epinephrine dosing when considering studies [13–16] of children and adults experiencing anaphylaxis from a variety of triggers. Therefore, experts now recommend that all patients at risk for anaphylaxis always carry two epinephrine doses [7]. Repeat dosing could be a result of biphasic reactions or inadequate treatment response to the initial dose. In prior work [15], our group reported that most patients received the second dose within 1 h of the first dose, suggesting that inadequate treatment response was the more frequent explanation. Studies [13,15] have also supported that older age and asthma may be associated with the receipt of additional epinephrine treatments, which may be a reflection of more severe anaphylaxis in these cases. Until further work is done to better define the risk factors for multiple doses, most experts advocate that all patients at risk for anaphylaxis always carry two doses.

Mode of delivery

With regard to the mode of administration, it has been recommended by most (but not all) current guidelines that epinephrine be given preferentially intramuscularly in the mid anterolateral aspect of the thigh [4,5[¶],7]. Accordingly, all current EAs are universally recommended to be injected in this anatomical location. This recommendation is based on observational studies [9,10] in children and adults that demonstrate that this mode results in optimal absorption. However, studies [17,18] using imaging modalities have found that the length of the epinephrine auto-injector needle is sometimes not long enough to reach muscular tissue in the thighs of obese individuals. 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. However, in a multicenter observational study [19[¶]] of children and adults with anaphylaxis because of food and stinging insects, obesity was not a risk factor in receiving multiple doses of epinephrine. Further work is needed to make definitive evidence-based recommendations on the ideal route of delivery and whether this recommendation applies for all individuals regardless of age, body habitus and other physiologic factors.

EPINEPHRINE AUTO-INJECTOR AVAILABILITY AND USE

All patients with a history of anaphylaxis who may potentially encounter the culprit allergen again

Table 1. Current indications for Epinephrine Auto-Injector Prescription [4,5*,6,7,12]

Definite
1. All patients with a history of anaphylaxis (any trigger)
2. All patients with a history of a systemic allergic reaction (any trigger)
3. Patients with IgE mediated food allergy and a history of asthma
4. Patients with IgE mediated food allergy to specific food triggers known to be associated with severe/fatal reactions (i.e. peanut, tree nuts, fish and shellfish)
Possible
1. Consider prescribing to all patients with IgE-mediated food allergy
2. Consider prescribing to patients at risk for anaphylaxis regardless of previous reaction history or specific allergic trigger
3. Special consideration should be given to patients in whom the details of the initial reaction are unclear and those who live in areas remote from acute medical care

outside of a healthcare setting should be prescribed an EAI. More recently, many guidelines recommend that all patients at risk for anaphylaxis (even in the absence of a history of anaphylaxis) be prescribed an EAI. Specifically, the most recent food allergy guidelines published in the USA in 2010 recommend considering an EAI prescription for all patients with IgE-mediated food allergy, especially those with a history of food allergy to peanuts, tree nuts, fish and shellfish and those with a concomitant history of asthma [7]. Detailed information on current prescription recommendations is outlined in Table 1.

Because of a combination of factors including changes in prescription recommendations, increasing anaphylaxis public awareness and likely an increase in the prevalence of anaphylaxis itself [20,21], there is evidence that prescriptions for EAIs are on the rise both in North America and worldwide [22,23*]. Specifically within the USA, Camargo *et al.* [22] reported that in 2004, there were 5.71 EpiPens prescribed per 1000 persons with evidence of regional variation in these prescriptions. Subsequently, there has been reported a 69% increase in U.S. prescriptions between 2003 and 2010 [23*]. In other parts of the world, the increase in epinephrine prescriptions has been even more striking with greater than 200% increase in Australia (1998–2002) [24] and a 1200% increase in the United Kingdom (1991–2004) [25].

Prescribing patterns

Despite these observations, there continue to be several areas identified that require improvement in both our prescribing practices and the subsequent availability of EAIs. Multiple studies [14–16,26,27] have illustrated deficiencies specifically in the disposition of anaphylaxis patients from the emergency department (ED) in this regard. In one of the first studies to address this important healthcare outcome in 2004, Clark *et al.* [26] reported that only

16% of patients discharged from 21 North American EDs with a food-related acute allergic reaction were prescribed self-injectable epinephrine. In more current reviews, this percentage has improved slightly (to approximately one third of patients), but continues to highlight a missed opportunity for emergency medical staff to provide patients with the means to appropriately manage potential future episodes of anaphylaxis [15,16,27]. The reported percentages are more reassuring among patients admitted to the hospital, but this most likely reflects a population of patients with more severe and readily recognizable presentations of anaphylaxis [14–16].

In settings outside of the ED, less data are available and also suggest a need for improvement. A recent survey from the UK indicates that prescribing decisions among both pediatricians and pediatric allergists are often inconsistent and vary with the type of allergen and level of parental anxiety [28]. Furthermore, there was a recent suggestion that health disparities exist in the prescribing patterns of EAIs. Specifically, peanut allergic children in Canada of higher socioeconomic status were reported to be more likely to be prescribed an EAI [29]. Finally, although the prevalence of EAIs is increasing in many countries, in 80% of the world's 195 countries, EAIs are not available at all [30].

Patient education and knowledge deficits

Once an EAI is prescribed, the patient should receive appropriate education on when and how to use it, including a clearly written emergency action plan. In the pediatric population, this education must also include consideration of when the responsibility may safely be transitioned to the child or teen [31*]. In order for an EAI to be effective, the device must be readily available to the patient, used promptly in the setting of anaphylaxis and administered correctly. Unfortunately, numerous studies [32–35] from the stinging insect hypersensitivity and food allergy

literature have clearly pointed toward deficiencies in all of these aspects of 'anaphylaxis readiness'. For example, studies [34–37] indicate that only 25–50% of patients actually carry their EAI with them. When specifically looking at school-aged children, multiple studies have pointed out potential issues related to access to EAI while in school. DeMuth and Fitzpatrick [35] reported based on questionnaire data that only 25% of school-aged children had an EAI available to them while at lunch versus slightly higher percentages in younger children. Parental EAI training improved the odds of EAI device availability while in school. Other studies have indicated that patients often possess expired EAI which highlight another area in which improvement in patient education is needed [34]. Although expired EAI do not lose all of their effect, clearly having an unexpired medication on hand is vastly preferable [38].

Even when patients do possess their EAI, studies indicate a reluctance to use the device. This assuredly can lead to delays or complete lack of administration of this potentially life-saving medication. Two separate surveys from adult and pediatric populations indicate that the majority of patients experiencing anaphylaxis did not use their EAI (73 and 83%, respectively) [39,40]. EAI are underused by patients for a number of reasons, including failure to recognize anaphylaxis, lack of understanding of when use of their EAI is appropriate and fear regarding its use.

Lastly, the literature points toward a lack of knowledge on how to use EAI both by patients and by their caregivers. Only one-third of patients were able to correctly demonstrate all of the steps of its use in a pediatric allergy clinic [34]. Unfortunately, healthcare providers [34,41] and school personnel [42,43] have also been shown to be deficient in knowledge about the correct administration of EAI. It should be noted that a step commonly evaluated in this literature was holding the device in place for 10 s after firing; however, a recent ex-vivo study [44] on epinephrine absorption suggested that holding device in place for 1 s might be just as effective. Regardless, additional efforts are clearly needed to optimize education of healthcare providers and patients on the use of EAI. This need for additional education may be further highlighted by the recent observations that owning an EAI was associated with poorer quality of life in children with food allergy [45].

ADVERSE EFFECTS

Mild transient pharmacologic effects can occur within minutes after epinephrine injection and can include anxiety, pallor, increased heart rate,

headache or dizziness. Other more serious adverse effects are rare when epinephrine is administered via EAI, but have been reported within the context of overdose and errors in intravenous infusion [46]. In general, when epinephrine is given appropriately, serious adverse effects are not a concern in otherwise healthy children and adolescents. However, given its cardiac effects, the benefits of administration of epinephrine in adult anaphylaxis patients with (or at risk for) coronary artery disease must be weighed against potential risks [1]. There are no absolute contraindications to the administration of epinephrine for anaphylaxis in any patient [6].

Accidental epinephrine digital injection is a known risk associated with the use of EAI [47–49]. In a state-wide report from 2010, Muck *et al.* [47] presented data from a cohort of 365 cases of accidental digital injection identified from the Texas Poison Center Network database over a 6-year period. Most cases had transient (<2 h), mild symptoms (pain, discoloration) and did not receive any pharmacologic therapy (77%). Reports of 'digital ischemia' were infrequent (3%) and all resolved with medical therapy. In a more comprehensive study [48] based on national of poison control and adverse event databases in the USA, a total of 15 190 unintentional injections from EAI were voluntarily reported between 1994 and 2007. Because the number of unintentional injections was observed to be increasing annually during this time, the authors called for increased education and improved EAI design.

NEW DIRECTIONS

Although the benefits of EAI in the emergency care of anaphylaxis in the community cannot be argued, there are several limitations to these devices. As discussed above, patients have demonstrated a reluctance to carry these devices with them and often hesitate to use them when needed. It has been suggested that less 'bulky' and more 'user-friendly' designs would help address these shortcomings. Furthermore, the risk of self-digital injection might be decreased by modifying the 'pen-like' designs of previously available EAI.

Attempts to address these limitations have led to the redesign of current devices and the development of new devices. Currently available devices are summarized in Table 2. In 2010, EpiPen introduced a newly designed device in order to attenuate presumed design-associated issues, such as self-digital injection. This new design included an asymmetrical shape, more clearly colored ends and needle safety guards. In a comparison study, 220 interns were asked to demonstrate use of either the new or old device. The authors report that the participants were not able to more frequently demonstrate

Table 2. Comparison of available epinephrine auto-injectors

	EpiPen	Twinject	Auvi-Q	AnaPen
Available doses (mg)	0.15, 0.3	0.15, 0.3	0.15, 0.3	0.15, 0.3, 0.5
Availability	USA, Worldwide	Canada	USA (Allerject in Canada)	Europe, Australia
Dimensions (length × width in cm)	15.2 × 2.5	14.6 × 1.6	8.6 × 5.1	16.8 × 1.9
Exposed needle length (cm)	1.3/1.48	1.29/1.32	1.27/1.57	1.30
Shelf-life	12–18 months	12–18 months	12–18 months	21–24 months
Cost (U.S. dollars) ^a	\$312.99	\$345.99	\$324.99	N/A
Needle protection	Yes	No	Yes	No
Special features		Two doses	Audio cues	
Manufacturer	Mylan Specialty L.P., USA	Amedra Pharmaceuticals, USA	Sanofi, USA	Lincoln Diagnostics, UK

^aCash price in the United States with no insurance coverage. Please note the actual cost will be variable based on numerous factors, including insurance coverage, rebates, etc.

the proper use of the newly designed EAI, but the unintentional injury rate was nine times lower with the new device [50].

Most recently, in February of 2013, a new EAI became available in the USA, Auvi-Q (Sanofi, Bridgewater, NJ, USA). With its compact, rectangular-shaped design and automated voice instructions that guide a user through the injection process, the manufacturers hope it will also address the shortcomings of earlier devices. Guerlain *et al.* [51,52] reported in two separate studies in 2010 that both healthcare professionals and patient participants preferred the design of the new device compared with the EpiPen and Twinject devices. Meanwhile, a comparison of two devices available in Europe, EpiPen and AnaPen, found no difference in the ability to correctly use these injectors, but maternal preference of AnaPen devices [53]. It should be noted that none of these studies used the new version of the EpiPen for comparison and therefore may not be a current, unbiased reflection of preference and usability of these current devices [54].

Finally, in another tactic to improve the public usability of epinephrine, sublingual epinephrine is currently being designed. Initial issues with bitter taste have been addressed. Current work in animal models reveals that sublingual epinephrine tablets have a similar bioavailability to epinephrine injected intramuscularly in the thigh [55^{*}]. Further studies will be required to determine whether this could be a suitable treatment option for patients with anaphylaxis in the community.

CONCLUSION

EAI's remain the cornerstone of treatment of anaphylaxis in the community because of their ability to rapidly deliver this potentially life-saving medication outside of a medical setting. Although the study of epinephrine is difficult because of practical

and ethical considerations, continued efforts are needed to establish evidence-based parameters for the delivery of this medication and to optimize education of healthcare providers and patients on the use of EAI's in the setting of anaphylaxis.

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Conflicts of interest

There are no conflicts of interest.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 459–460).

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