

Epinephrine and its use in anaphylaxis: current issues

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Current Opinion in Allergy and Clinical Immunology 2010, 10:354–361

Purpose of review

Epinephrine is a life-saving medication in the treatment of anaphylaxis, in which it has multiple beneficial pharmacologic effects. Here, we examine the evidence base for its primary role in the treatment of anaphylaxis episodes in community settings.

Recent findings

We review the practical pharmacology of epinephrine in anaphylaxis, its intrinsic limitations, and the pros and cons of different routes of administration. We provide a new perspective on the adverse effects of epinephrine, including its cardiac effects. We describe the evidence base for the use of epinephrine in anaphylaxis. We discuss the role of epinephrine auto-injectors for treatment of anaphylaxis in community settings, including identification of patients who need an auto-injector prescription, current use of auto-injectors, and advances in auto-injector design. We list reasons why physicians fail to prescribe epinephrine auto-injectors for patients with anaphylaxis, and reasons why patients fail to self-inject epinephrine in anaphylaxis. We emphasize the primary role of epinephrine in the context of emergency preparedness for anaphylaxis in the community.

Summary

Epinephrine is the medication of choice in the first-aid treatment of anaphylaxis in the community. For ethical reasons, it is not possible to conduct randomized, placebo-controlled trials of epinephrine in anaphylaxis; however, continued efforts are needed towards improving the evidence base for epinephrine injection in this potentially fatal disease.

Keywords

adrenaline, anaphylaxis, epinephrine, epinephrine auto-injectors, food allergy, insect venom allergy

Curr Opin Allergy Clin Immunol 10:354–361
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1528-4050

Introduction

Epinephrine is a natural body constituent, comprising approximately 80% of the catecholamines in the human adrenal medulla. During sudden frightening or life-threatening situations, endogenous epinephrine is released from this site and affects sympathomimetically innervated structures all over the body. The heart rate accelerates and the force of cardiac contractions increases. The blood pressure rises. Blood flow is redistributed from the skin and subcutaneous tissue to the skeletal muscles, splanchnic circulation, and brain. The bronchi and pupils dilate. Oxygenation increases, the blood glucose rises, and the body is prepared for 'fight or flight' [1].

Early in the 20th century, epinephrine (adrenaline) was synthesized for use in humans. Until mid-century, it was used primarily in asthma treatment, in which it has been largely replaced by selective beta-2 adrenergic agonists such as albuterol (salbutamol). Epinephrine remains widely used for treatment of postintubation croup and viral croup, in which it is given by face mask and nebu-

lizer. It is ubiquitously used in surgery, where dilute solutions (e.g. 1 : 100 000) provide hemostasis and/or prolong the duration of action of concomitantly administered local anesthetics [1].

In the 1960s, after publication of several case series involving people in community settings with anaphylaxis triggered by foods, medications, and stinging insect venoms [2], syringes prefilled with epinephrine were introduced so that in the absence of a healthcare professional, those without medical training could inject epinephrine readily. In 1980, epinephrine auto-injectors were introduced.

Currently, the World Health Organization (www.who.int) and the World Allergy Organization consider epinephrine to be an essential medication for anaphylaxis treatment [3].

All anaphylaxis guidelines recommend injection of epinephrine as the first-line medication of choice in anaphylaxis in community settings as well as in healthcare

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DOI:10.1097/ACI.0b013e32833bc670

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IPR2025-00874

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settings [4–6]. Epinephrine in ampule formulations is universally available worldwide, even in low-resource countries [7]. It is widely prescribed for anaphylaxis [8*,9,10]; indeed, in some countries, the increase in epinephrine prescribing is disproportionately higher than the increase in the rate of occurrence of anaphylaxis [11].

Practical pharmacology of epinephrine

The pharmacology of epinephrine is summarized in Table 1 [1,2,8*,12].

Beneficial effects

In patients with anaphylaxis, epinephrine has potent life-saving α -1 adrenergic vasoconstrictor effects on the small arterioles and precapillary sphincters in most body organ systems [1]. Through vasoconstriction, it decreases mucosal edema, thereby preventing and relieving upper airway obstruction and increases blood pressure, thereby preventing and relieving shock. Its β -1 adrenergic effects lead to increased rate and force of cardiac contractions. Its β -2 effects lead to increased bronchodilation and decreased release of histamine, tryptase, and other mediators of inflammation from mast cells and basophils [1].

Routes of administration

The pros and cons of epinephrine administration through various routes are summarized in Table 2 [1,8*,12–18,19*,20*]. Intramuscular injection into the mid-anterolateral aspect of the thigh is recommended as the initial route of choice in most [4,5] but not all [6] anaphylaxis guidelines. Epinephrine has a vasodilator effect in skeletal muscle [1], which facilitates rapid absorption into the central circulation and prompt pharmacologic effects [12–16].

In contrast, the powerful vasoconstrictor effect of epinephrine injected into subcutaneous tissue potentially delays epinephrine absorption from this site and onset of pharmacologic effects [1]. This delay may be clinically relevant in anaphylaxis [17].

Intravenous infusion of epinephrine is occasionally needed in the community, for example, when a patient with anaphylaxis in a physician's office does not respond to intramuscular epinephrine or experiences profound hypotension or shock. An intravenous bolus dose is needed if cardiorespiratory arrest has occurred. In such patients, paradoxically, venous access might be difficult. Iatrogenic overdosing through the intravenous route is not uncommon, contributing to the perception that epinephrine has a narrower benefit-to-risk ratio when injected intravenously than when given by other routes in anaphylaxis [16,20*].

Intrinsic limitations

Soon after epinephrine was introduced for clinical use, its intrinsic pharmacologic limitations became apparent (Table 1). It cannot be given orally, as swallowed epinephrine is metabolized by catechol-*o*-methyltransferase in the wall of the gastrointestinal tract and by monoamine oxidase in the gastrointestinal tract wall and in the liver [1]. Regardless of the route of administration, epinephrine has a short duration of action and a narrow therapeutic index; that is, its benefits cannot be separated from its adverse effects [8*,12,15]. It also has biphasic pharmacologic effects; for example, a low dose might have the opposite effect to that which is intended and might lead to vasodilation and increased release of mediators of inflammation [1,12]. In addition, epinephrine formulations in solution for injection have a short shelf-life (typically 12–18 months) and epinephrine degradation products are inactive [12].

Table 1 Practical pharmacology of epinephrine

Beneficial effects	
Through α -1 adrenergic receptors:	vasoconstriction, increased peripheral vascular resistance (most organs) ^a , increased blood pressure and relief of hypotension and shock; decreased mucosal edema and relief of upper airway obstruction and angioedema/hives
Through α -2 adrenergic receptors:	decreased insulin release
Through β -1 adrenergic receptors:	increased heart rate and force of cardiac contractions ^b
Through β -2 adrenergic receptors:	bronchodilation, vasodilation, decreased release of mediators (histamine, tryptase, and others) ^c
Adverse effects	
Through α -1 adrenergic receptors:	pallor, headache
Through β -1 adrenergic receptors:	palpitations
Through β -2 adrenergic receptors:	tremor, vasodilation ^c , increased release of mediators ^c
Through central CNS stimulation:	anxiety
Intrinsic limitations	
Rapidly metabolized when given by any parenteral route (half-life in children after intramuscular injection, 43 min)	
Inactivated in the gastrointestinal tract when swallowed	
Therapeutic dose in anaphylaxis is similar to the dose that leads to mild transient adverse effects ^d	
Epinephrine in solution breaks down to inactive substances over months to years, even when stored in a sealed container (no exposure to oxygen) in acidic solution containing antioxidants.	

CNS, central nervous system. Data from [1,2,8*,12].

^aVasodilator effect in skeletal muscle through β -2 receptors.

^bLeads to increased coronary artery blood flow.

^cEpinephrine has complex biphasic effects; for example, at very low doses, unintended effects such as vasodilation or increased mediator release may occur.

^dRefers to initial dose of 0.01 mg/kg to a maximum of 0.3–0.5 mg (adult) and 0.3 mg (child).

Table 2 Epinephrine: pros and cons of different routes of administration in anaphylaxis^a

Intramuscular	
Pros	- Epinephrine has a vasodilation effect in skeletal muscle - Skeletal muscle is highly vascular, leading to rapid absorption - Drug injected into vastus lateralis reaches the central circulation promptly - Peak pharmacologic effects are achieved promptly - Benefit-to-risk ratio perceived to be optimal when this route is used for first-aid treatment - Most commonly recommended route worldwide
Cons	- Currently available auto-injector needle lengths and gauges are not optimal for intramuscular injection in overweight or obese people - Not effective if muscle perfusion is poor or absent due to shock or cardiorespiratory arrest
Subcutaneous	
Pros	Readily accessible sites of injection
Cons	- Epinephrine, even in a 1:100 000 dilution, leads to vasoconstriction/blanching of subcutaneous tissue^c - Epinephrine slows its own absorption from subcutaneous tissue^c - Subcutaneous tissue is poorly vascularized compared with skeletal muscle^b - Low tissue epinephrine levels potentially lead to increased vasodilation and increased mediator release - Rapid epinephrine absorption is more critical in anaphylaxis than in asthma
Intravenous	
Pros	Optimal route of administration for patients with severe anaphylaxis who have not responded to intramuscular epinephrine and/or are experiencing profound hypotension or shock, or in whom cardiorespiratory arrest is imminent
Cons	- Establishing a peripheral intravenous route for epinephrine administration may be difficult in the above patients - Narrower benefit-to-risk ratio than epinephrine administered by other routes, partly attributed to iatrogenic error - For safe administration in hypotension or shock, it is optimally given through an infusion pump and central line by physicians trained and experienced in continuous dose titration of vasopressors against continuously monitored heart rate and function, blood pressure, and oxygenation - Errors in epinephrine dosing combined with errors in assessment of cardiac rate and function and blood pressure can be catastrophic for the patient

Data from [1,8^{*},12–18,19^{*},20^{*}].

^a Other routes of administration include inhalation through a metered-dose inhaler or face mask/nebulizer and compressor; by this route, epinephrine might relieve respiratory symptoms, but it is difficult to achieve sufficiently high tissue concentrations to relieve other systemic anaphylaxis symptoms.

^b After subcutaneous injection, median time to peak epinephrine levels is 34 min. Median time to cardiac arrest in anaphylaxis is 5–30 min, depending on the anaphylaxis trigger.

^c Epinephrine is widely used in surgery to provide hemostasis and to slow absorption of local anesthetics from skin, mucosa, subcutaneous tissue, and submucosal tissue.

Adverse effects

Mild transient pharmacologic effects such as pallor, tremor, anxiety, palpitations, headache, and dizziness occur within minutes after epinephrine injection [12–15]. These effects confirm that a therapeutic dose has been given (Table 1). Serious adverse effects such as pulmonary edema or hypertension potentially occur when epinephrine is given in overdose by any route, most commonly after an intravenous bolus injection, an overly rapid intravenous infusion, or an erroneous intravenous injection of a 1 mg/ml (1:1000) epinephrine solution instead of an appropriately diluted 0.1 mg/ml (1:10 000) epinephrine solution [4,5,16,20^{*}].

Epinephrine and the heart

The heart is underrecognized as a target organ in anaphylaxis. Mast cells are present throughout the myocardium, between muscle fibers, around blood vessels, and in the coronary artery intima. In patients with coronary artery disease, mast cells are also present in the atherosclerotic plaques, where they contribute to atherogenesis [21]. Histamine, leukotrienes, platelet-activating factor, and other mediators of inflammation released after mast cell stimulation potentially lead to coronary

artery spasm [21]. Patients of any age, including children, with anaphylaxis can present with angina or myocardial infarction due to vasospasm [22,23^{*}]. In middle-aged or elderly patients, these acute coronary syndromes potentially occur either through vasospasm or through acute plaque rupture and thrombus formation [22,23^{*}].

Some patients taking beta-adrenergic blockers or angiotensin-converting enzyme (ACE) inhibitors are at increased risk of severe or fatal anaphylaxis [24,25^{*}]. In an observational study of 962 patients with stinging insect venom allergy, 21% of whom developed severe systemic allergic reactions defined as shock, loss of consciousness, or cardiopulmonary arrest, ACE inhibitors were identified as one of the significant risk factors for severe anaphylaxis [25^{*}].

In middle-aged or elderly patients who might have subclinical coronary artery disease and in patients with diagnosed coronary artery disease, concerns about the potential cardiac effects of epinephrine should be weighed against the cardiac risks of untreated anaphylaxis. In these patients, it is important to remember that epinephrine injection usually enhances blood flow in the

coronary arteries through its beta-2 adrenergic actions, which leads to increased myocardial contractility and increased duration of diastole compared with systole (Table 1) [1,8[•]]. There are no absolute contraindications to epinephrine use in anaphylaxis.

Evidence base for epinephrine use in anaphylaxis

No randomized controlled trials that meet optimal standards have been published for any medication used in the treatment of acute anaphylaxis; however, the evidence base for epinephrine injection in anaphylaxis is stronger than the evidence base for use of H₁-antihistamines, H₂-antihistamines, or glucocorticoids in the initial treatment of this disease [26[•],27,28]. Recommendations for prompt epinephrine injection are based on a century of clinical use [1] and on fatality studies [17,29–31], epidemiologic studies [9,10], and prospective studies [12–15,32,33]. The latter include both dramatic observational nonrandomized uncontrolled studies in patients actually experiencing anaphylaxis at the time of the investigation [32,33] and randomized controlled studies in patients not experiencing anaphylaxis at the time of the investigation [12–15]. In vitro studies relevant to anaphylaxis [1,12,34] and studies in animal models of anaphylaxis [1,12,35] have also been performed.

Delayed injection of epinephrine is potentially associated with fatal anaphylaxis [17,29–31]. In a study of 164 patients with fatal anaphylaxis, the median time from initial symptom to cardiorespiratory arrest was 5 min in iatrogenic anaphylaxis, 15 min in venom-triggered anaphylaxis, and 30 min in food-triggered anaphylaxis [17]. In this and other fatality studies, a small percentage of patients died despite receiving an injection of epinephrine before they experienced cardiac arrest. The body weight and, therefore, the adequacy of the epinephrine dose on a mg/kg basis were either not known or not reported in these patients. For many of them, the precise time elapsed from the first symptom to epinephrine injection, and whether the injection was administered correctly were also not known or not reported [17,29–31].

Delayed injection of epinephrine might be one of several factors contributing to biphasic anaphylaxis, defined as symptom recurrence 1–72 h (usually within 8 h) after resolution of the initial symptoms, without ongoing or further exposure to the anaphylaxis trigger [8[•],36[•],37[•]].

Epinephrine auto-injectors for anaphylaxis in community settings

For patients at risk of anaphylaxis recurrence in the community, epinephrine should preferably be prescribed in an auto-injector formulation.

Identification of patients who need an epinephrine auto-injector

Physicians generally agree that epinephrine auto-injectors should be prescribed for patients with a history of upper or lower respiratory symptoms, hypotension, or shock in anaphylaxis, those with a history of anaphylaxis from certain triggers including foods (such as peanut, tree nuts, and shellfish), insect stings or exercise, and those with idiopathic anaphylaxis [16,38].

Physicians face a quandary as to whether to prescribe epinephrine auto-injectors for other types of patients, for example, those with a history of acute generalized hives after exposure to a known trigger [38]. In this situation, it might be helpful to recall that some patients dying from anaphylaxis, for whom epinephrine auto-injectors had not been prescribed, had experienced mild anaphylaxis symptoms on previous occasions before their demise. It might also be helpful to consider patient-specific risk factors that increase the likelihood of severe or fatal anaphylaxis [8[•]]. These include age of the patient (infants, teens, the elderly), comorbid diseases, including asthma, cardiovascular disease, and mastocytosis, and concurrent medications, including beta-blockers and ACE inhibitors. Other patients might be at increased risk because of defects in mediator degradation pathways; abuse of ethanol or other chemical substance; interruption of routine; living alone or in a remote area, or lacking reliable transportation or means of communication [2,8[•], 12,24,25[•]].

Use of epinephrine auto-injectors

Currently, the optimal way of providing first-aid treatment with epinephrine (adrenaline) for anaphylaxis in the community is through an auto-injector [2–8[•],12,16]. The first-aid dose of epinephrine, 0.01 mg/kg of a 1 mg/ml (1 : 1000) formulation to a maximum dose of 0.5 mg in an adult or 0.3 mg in a child, is based on tradition and clinical consensus rather than on randomized controlled trials. Most anaphylaxis guidelines recommend injecting it from an auto-injector intramuscularly in the mid-antrolateral aspect of the thigh [3–5]. Fatality studies suggest that in some patients, there is only a brief window of time during which the low first-aid dose of epinephrine is effective [17,29–31]. If anaphylaxis has progressed to cardiopulmonary arrest and resuscitation is required, this low dose is unlikely to be effective, as the dose for resuscitation is 1 mg, administered as an intravenous bolus [8[•]].

On the basis of clinical consensus, the epinephrine dose can be repeated every 5–15 min, as needed [3,4,6]. On the basis of a report in which ten deaths from anaphylaxis in a community setting occurred within minutes of patients being placed or maintained in the upright position, which led to the empty inferior vena cava/empty

ventricle syndrome [39], patients should remain supine or recumbent after receiving an epinephrine injection.

Multiple doses of epinephrine are needed by patients with severe or protracted anaphylaxis symptoms that are not relieved by the initial dose and by those with biphasic or multiphasic anaphylaxis. The number of patients reported to require more than one dose of epinephrine differs from study to study. In two prospective studies in which all or most patients with anaphylaxis after allergen immunotherapy injections received epinephrine injections promptly [36*,37*], although biphasic reactions occurred in 23 and 10% of the patients, respectively, additional epinephrine was not given to any patient. In a retrospective review [40] of emergency department records, 13% of patients with anaphylaxis from all triggers received additional epinephrine. In a retrospective review [41] of emergency department records of children with food-related anaphylaxis, 12% received more than one dose of epinephrine.

Advances in epinephrine auto-injector design

In most countries, there are only two fixed epinephrine doses (0.15 and 0.3 mg) available in auto-injector formulations [42] [EpiPen (Dey LP, Napa, California, USA); Adrenaclick and Twinject (Sciele, Division of Shionogi, Japan); and Anapen (Lincoln Medical, Salisbury, Wiltshire, UK)]. It is, therefore, difficult to dose infants and young children weighing less than 15 kg accurately, or to dose large teens and adults accurately. Also, in most countries, the auto-injectors available have a relatively short needle length and might not achieve intramuscular

injection in some adults [18] or even in some children [19*], in whom the distance from the skin to the vastus lateralis muscle has been measured by using computed tomographic scans of the thigh [18] or ultrasound of the thigh [19*]. In addition, most epinephrine auto-injectors available have a shelf-life of only 12–18 months [12].

Progress is being made in overcoming some of these limitations (Table 3) [43]. In the United Kingdom, other European countries, and Australia, a 0.5 mg epinephrine dose Anapen is now available in addition to the 0.15 mg dose and the 0.3 mg dose. The 0.5 mg dose Anapen has a maximum shelf-life of 24 months. In Canada and the United States, a re-designed EpiPen is now available. This device is intuitively easier to hold correctly, the 'needle' end is clearly labeled with words and an arrow, and the needle is automatically covered after injection.

Reasons for lack of use of epinephrine auto-injectors and apparent lack of response

Epinephrine auto-injectors are underused by patients for a variety of reasons, as outlined in Table 4 [8*,12,38,42, 44–46]. In some countries, they are not available [42]. In others, they are not affordable [42] or not prescribed when indicated, for example, at the time of discharge from an emergency department after treatment for an acute anaphylaxis episode [44], or because previous reactions were considered to be mild [38]. Existing alternatives to auto-injectors cannot be depended upon to produce high tissue concentrations of epinephrine rapidly [8*,12,34]. These include drawing up epinephrine from an ampule (takes too long and the dose is often

Table 3 Epinephrine auto-injectors^a

	EpiPen	Adrenaclick ^b	Anapen
Doses (mg)	0.15, 0.3	0.15, 0.3	0.15, 0.3, 0.5
Excipients			
Sodium chloride	6 mg	1.3/2.6 mg ^c	Present; mg n/a
Sodium metabisulfite	1.67 mg	Bisulfite 0.225/0.45 mg	Present; mg n/a
Other	HCl	Chlorobutanol 0.75/1.5 mg	HCl
Exposed needle length (cm)	1.3/1.48	1.29/1.32	1.30
Needle gauge (G)	22	25	27
Needle protection	Yes	No	No
Description			
Weight (g)	75.5 (with case)	45.4 (with case)	28.8
Length (cm)	15.6 (with case)	16 (with case)	16.9
Shelf-life (months) ^d	12–18	12–18	21 (0.15 mg), 24 (0.3 mg, 0.5 mg)
Availability ^e	'Worldwide'	USA, Canada	Europe, Australia
Cost ^f	Variable	Variable	Variable
Number of doses per auto-injector	1	1	1

HCl, hydrochloric acid; n/a, not available.

^a Several novel epinephrine auto-injectors are in development, including INT01/INT02 that measures 8.6 x 5.1 x 1.6 cm [43].

^b Adrenaclick and Twinject are similar auto-injectors except that Adrenaclick contains one epinephrine dose and Twinject contains two doses.

^c Where two numbers are shown, the first number refers to the 0.15 mg dose and the second number refers to the 0.3 mg dose.

^d Stored in original sealed container, protected from light, at room temperature 20–25 °C with excursions permitted to 15–30 °C; 'do not refrigerate, do not freeze'.

^e See text for details; at time of publication, auto-injectors were available in 45/195 countries worldwide and availability was gradually improving.

^f Cost of one auto-injector to the patient depends on many different factors. Dispensing fees and taxes may be added to the base (wholesale) cost. Government subsidies or private insurance or rebates might decrease the price; however, age restrictions may apply to subsidies (e.g. epinephrine auto-injectors are available at no charge to children less than 16 years of age in the United Kingdom), and additional factors such as co-pays and limitations on number of auto-injectors per year might apply to private insurance.

Table 4 Epinephrine auto-injectors in anaphylaxis: reasons for lack of use and apparent lack of response

Lack of use of epinephrine auto-injectors (common)
Not available for purchase in many countries
Not prescribed by physician
Not affordable
Prescription not filled or picked up
Not accessible when anaphylaxis occurred
Not used because:
Patient used another medication, e.g. H ₁ -antihistamine or asthma puffer ^a
Reaction seemed to be mild
Reaction seemed to improve quickly
Patient was unsure when to inject
Patient was afraid to inject
Epinephrine was past expiry date
Previous systemic allergic reaction improved quickly ^b
Apparent lack of response to epinephrine (uncommon)
Rapid progression of anaphylaxis
Empty ventricle syndrome
Patient taking another medication ^c that interfered with epinephrine effect
Epinephrine injected too late
Epinephrine dose too low
On a mg/kg basis for body weight of patient
Due to auto-injector being past the expiry date
Delayed absorption
Route of injection not optimal
Site of injection not optimal
Epinephrine injected using incorrect technique, e.g. not enough force
Adverse reaction to sodium metabisulfite preservative in the epinephrine solution (rare)

Data from [8^{*},12,38,39,42,44–46].

^a H₁-antihistamines relieve hives and flushing, but do not relieve respiratory symptoms or shock. Beta-2 adrenergic agonists relieve bronchospasm but do not relieve upper airway obstruction or shock.

^b Subsequent episodes in the same patient may be less, equally, or more severe.

^c For example, beta-adrenergic blocker by any route of administration (oral, ophthalmic solution), or angiotensin-converting enzyme inhibitor.

inaccurate) [12], using an unsealed syringe prefilled with epinephrine by the patient's physician (shelf-life is only 3–4 months) [34], or using a chlorofluorocarbon-containing epinephrine metered-dose inhaler [difficult to inhale enough epinephrine to relieve nonrespiratory symptoms (20 puffs needed in a child; 30 puffs needed in an adult)] [12].

Many patients do not have their epinephrine auto-injector(s) with them at the time an anaphylaxis episode occurs [45^{*}]. In school settings, many children are at risk for delay in anaphylaxis treatment because of restricted access to their epinephrine auto-injectors [46]. Other reasons for not using an epinephrine auto-injector in the treatment of anaphylaxis in the community are listed in Table 4.

Failure to respond to epinephrine injection is uncommon. Potential reasons for this include rapid progression of anaphylaxis, delay in epinephrine injection, delayed absorption of epinephrine due to injection through a

suboptimal route or site, the empty ventricle syndrome as previously described, or concurrent use of a medication that interferes with optimal epinephrine effect [8^{*},12] (Table 4).

Epinephrine, the cornerstone of emergency preparedness

Anaphylaxis education about when, why, and how to use an epinephrine auto-injector, remains critically important. Healthcare professionals need to be trained to use epinephrine auto-injectors in order to train those at risk for anaphylaxis and their caregivers how to use them correctly and safely [8^{*},47]. More than 15 000 unintentional injections from epinephrine auto-injectors, for example, into a finger, thumb, or hand were voluntarily reported to the American Association of Poison Control Centers from 1994 to 2007 [48^{*}]. These unintentional injections potentially lead to injury and to the so-called 'lost dose hazard' [47,48^{*}]. The latter is defined as the outcome of an anaphylaxis episode in someone whose epinephrine dose is completely lost when unintentionally self-injected by their caregiver, or, partially lost when someone with anaphylaxis unintentionally self-injects epinephrine into their own finger, thumb, or other body part, leading to profound local vasoconstriction and delayed epinephrine absorption.

Epinephrine auto-injectors should be prescribed along with a personalized anaphylaxis emergency action plan [2,8^{*}] that lists common signs and symptoms of anaphylaxis, and instructs the patient to inject epinephrine promptly, then call emergency medical services or go to an emergency department. Many different anaphylaxis emergency action plans are in use; however, none of them has been validated for efficacy or cost-effectiveness [49]. Medical identification jewelry (e.g. Medic Alert, Turlock, California, USA) should be worn at all times by patients at risk. A personalized anaphylaxis information card is available (www.aaaai.org) for carrying in a wallet or backpack [2].

An important aspect of long-term risk reduction in anaphylaxis involves follow-up of the patient at regular intervals. Such visits should include reassessment of his or her ability to use an epinephrine auto-injector correctly and coaching with regard to any improvements needed. They also offer the opportunity to improve the management of comorbidities such as asthma or cardiovascular disease, discuss the benefits and risks of concurrent medications such as beta-blockers and ACE inhibitors, review strategies for avoidance of allergen triggers, and, if relevant, begin or continue immunomodulation such as subcutaneous immunotherapy to prevent stinging insect venom anaphylaxis [8^{*}].

Future role of epinephrine in anaphylaxis

No new medications for the treatment of an acute anaphylaxis episode are on the horizon. Novel epinephrine auto-injectors are in development [43], as are novel epinephrine formulations for administration through non-invasive transcutaneous, intranasal, or sublingual routes [50].

The World Health Organization (www.who.int) and the World Allergy Organization [3], as well as all anaphylaxis guidelines [4–6], state that epinephrine injection is fundamentally important in anaphylaxis management. Placebo-controlled trials of epinephrine are, therefore, clearly unethical. Recommendations for the maximum initial dose of epinephrine or the route of injection differ from one guideline to another; therefore, in the future, consideration might be given to the possibility of conducting randomized controlled trials comparing different first-aid epinephrine doses or different routes of injection [51].

Conclusion

Epinephrine, a century-old drug with multiple beneficial pharmacologic effects, remains the medication of first choice for the treatment of anaphylaxis. For ethical reasons, it is not possible to conduct randomized placebo-controlled trials of epinephrine in anaphylaxis; however, continued efforts are needed towards improving the evidence base for epinephrine injection in this potentially fatal disease.

Acknowledgement

We acknowledge the assistance of Lori McNiven.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 404).

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