



Epinephrine in anaphylaxis: doubt no more

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Purpose of review

The purpose of this manuscript is to review the literature in support of epinephrine (adrenaline) as first line of therapy of anaphylaxis, not H-1 antihistamines or corticosteroids.

Recent findings

The purpose of this review is to assess that epinephrine has a quick onset of activity and rapidly antagonizes multiple mediators that are active in anaphylaxis. Epinephrine has maximal pharmacodynamic effect within 10 min of intramuscular administration into the thigh. As epinephrine has a narrow therapeutic window, prefilled epinephrine auto-injectors are available. There are weight-appropriate doses of epinephrine available with auto-injectors that are prefilled with 0.15, 0.30 and 0.50 mg. In addition, needle lengths vary from 1.17 to 2.50 cm. Different doses and needle lengths are available for paediatric and adult patients, especially obese patients to ensure intramuscular delivery in the thigh.

Summary

Failure to administer epinephrine promptly has resulted in fatalities. Education about anaphylaxis and prompt treatment are critical for patients and their caregivers.

Keywords

adrenaline, anaphylaxis, auto-injector, intramuscular, subcutaneous

INTRODUCTION

For many years, clinicians and scientists have varied on how to better define anaphylaxis. There are still mild variations on the definition. The National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) definition of anaphylaxis proposed clinical diagnostic criteria [1]. The World Allergy Organization (WAO) definition divided anaphylaxis into immunologic, nonimmunologic and idiopathic causes [2^{***}]. The International Consensus on Food Allergy (ICON) describes IgE-mediated, cell-mediated and a combination of the above two process [3]. Yet, all the international organizations have one common recommendation: once anaphylaxis is diagnosed, epinephrine (adrenaline) is the first-line treatment. Delays in administration have been associated with fatalities.

Epinephrine was first described by John Abel, a pharmacologist, in 1897 [4]. He extracted a chemical from adrenal glands and named it epinephrine, from the Greek for 'on top of the kidneys'. Then in 1901, Jokichi Takamine purified a chemical from adrenal glands as well and called it adrenaline, from the Latin for 'on top of the kidneys'. Since then, the names epinephrine and adrenaline have been used interchangeably.

TREATMENT OF ANAPHYLAXIS

Epinephrine is the drug of choice for anaphylaxis on the basis of multiple international guidelines. Yet, many clinicians are using alternative medications such as H-1 antihistamines, H-2 antihistamines and corticosteroids to treat anaphylactic events. Diphenhydramine is one of the most common first-line medications given to patients in the Emergency Department. Yet, oral diphenhydramine takes up to 80 min for 50% suppression of the histamine flare and 52 min if administered intramuscularly (i.m.) [5]. Corticosteroids are the second most common medication administered in spite of the fact that they have a slow onset of action. Dexamethasone administered topically by iontophoresis can produce suppression of the histamine-induced

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wheal at 30 min [6]. But its onset of action via systemic routes of administration is far slower [7–9]. Although H-2 antihistamines are administered in combination with H-1 antihistamines for the initial treatment of anaphylaxis [10], a Cochrane review found no definitive evidence for or against the use of H-2 antihistamines in this setting [11]. The onset of action of H-2 antihistamines is also slower than that of epinephrine, and thus they remain a second-line therapy for anaphylaxis [1,2²²].

Epinephrine is the first line of therapy because it has a maximal pharmacodynamic effect within 10 min of i.m. administration into the thigh [12,13]. In addition, it acts on numerous receptors to antagonize the multiple pathologic effects of the mediators released during an anaphylactic episode as opposed to, for example antihistamines, which block the activity of only one mediator. Prompt administration is crucial, and a delay in administration has been associated with fatalities [14]. In addition, guidelines recommend repeating dose after 5–15 min if there is inadequate response with the first dose [1,2²²]. Therefore, many physicians recommend those patients at risk of anaphylaxis to have two epinephrine auto-injectors at all times.

PHARMACOKINETICS OF EPINEPHRINE

Evidence from clinical pharmacology and epidemiologic studies support the use of epinephrine in the treatment of anaphylaxis. The current recommendation on the use of epinephrine for the treatment of anaphylaxis includes both subcutaneous and i.m. administration. It is believed that early onset of high plasma and tissue epinephrine concentration appear to be critical for the reversal of hypotension and for survival in the early treatment of anaphylaxis. Studies have compared the pharmacokinetics and pharmacodynamics of epinephrine administered by the subcutaneous (in the arm) and i.m. (via the deltoid and the vastus lateralis muscle) routes. Intramuscular administration (via the vastus lateralis, but not the deltoid) results in quicker time to peak plasma concentration (T_{max}); 8 min for i.m. in the vastus lateralis muscle vs. 34 min for subcutaneous delivery [12,13]. In addition, i.m. via the vastus lateralis muscle results in higher peak plasma concentration (C_{max}) than the subcutaneous or deltoid route. In adults, there was no significant difference between time to peak plasma levels subcutaneously and deltoid injections [12]. Therefore, i.m. into the vastus lateralis, based on our best available data, appears to be the preferred route of administration of epinephrine in the emergency setting.

DOSING IN CHILDREN AND ADULTS

The recommended dose for epinephrine is 0.01 mg/kg of a 1 mg/ml (1:1000) dilution to a maximum dose of 0.5 mg in an adult or 0.3 mg in a child. If there is inadequate response, the dose can be repeated every 5–15 min. Currently, there are multiple commercially available prefilled epinephrine auto-injectors for outpatient use. It is available in 0.15, 0.30 and 0.50 mg epinephrine doses in select countries. The prefilled dose makes it effective for prevention of accidental overdosing and provides for the ease of administration by the patient or caregiver. It is recommended that children weighing 10–25 kg should receive a 0.15 mg epinephrine auto-injector. Those who weigh more than 25 kg should use the 0.30 mg dose [1,3]. Yet, there are concerns that an infant may be overdosed with the 0.15 mg auto-injector if their weight is less than 10 kg. Some clinicians support drawing up epinephrine through an ampule with syringe in these children. However, in the outpatient setting, it seems more prudent to use an auto-injector rather than syringe and ampule to minimize the chance of an incorrect dose.

There are concerns that the 0.30 mg epinephrine auto-injector may be an inadequate dose for some adults. In the early epinephrine literature, adult patients with asthma were treated with 1.0 mg of epinephrine [15]. Prior to automatic injectors, there were commercially available preloaded injectors with 0.50 mg of epinephrine for treatment of anaphylaxis. But when the auto-injector was introduced more than 20 years ago, it was available only in 0.15 and 0.30 mg doses. Until recently, these doses have been the only two available. Now there is an epinephrine auto-injector with a 0.5 mg for adults in Europe.

NEEDLE LENGTH OF AUTO-INJECTORS

In addition, needle lengths vary from 1.17 to 2.5 cm on the basis of different manufacturers (Table 1) [16–18]. There is no explanation on how the needle length of approximately 1.43 cm was chosen. In the United States military, auto-injectors were first developed for use in chemical and biological warfare. A pralidoxime chloride containing auto-injector has a needle length of 2.2 cm. Researchers thought that 2.2 cm would be needed for a healthy soldier wearing a thick protective chemical suit. A longer needle is necessary to penetrate two layers of clothing: the chemical suit and the soldier's uniform. Presumably, the producers of commercial products decided that a shorter needle length would be appropriate, as patients do not wear chemical suits. Recently, a commercial auto-injector with

Table 1. Epinephrine auto-injectors

Children auto-injector	Manufacturer	Needle length (cm)
Adrenaclick 0.15 mg	Ameda Pharmaceuticals LLC	1.17
Anapen 0.15 mg	Lincoln Medical Ltd	1.27
Auvi-Q 0.15 mg	Sanofi-Aventis LLC	1.27
Emerade 0.15 mg	Namtell AB	1.6
Epipen 0.15 mg	Mylan Inc.	1.27
Jext 0.15 mg	ALK-Abello	1.3

Adult auto-injector	Manufacturer	Needle length (cm)
Adrenaclick 0.30 mg	Ameda Pharmaceuticals LLC	1.17
Anapen 0.30 mg	Lincoln Medical Ltd	1.27
Auvi-Q 0.30 mg	Sanofi-Aventis LLC	1.57
Emerade 0.30 mg	Namtell AB	2.5
Emerade 0.50 mg	Namtell AB	2.5
Epipen 0.30 mg	Mylan Inc.	1.43–1.59 ^a
Jext 0.30 mg	ALK-Abello	1.5

^aEpipen has different needle lengths as reported by different published manuscripts. Song *et al.* [16] report 1.43 cm. Tsai *et al.* [17] report 1.52 cm. Bhalla *et al.* [18] report 1.59 cm.

2.5 cm needle became available in select European countries. It was developed with the thought in mind that it might offer an advantage (in reaching the muscle) when the injector was administered to an obese patient.

SIGNIFICANCE OF PROPER TISSUE DELIVERY

The Center for Disease Control's National Health and Nutrition Examination Survey states that the prevalence of obesity remains high and continues to rise in select populations in the United States [19]. As obesity continues to rise, there is concern that the needle length of an auto-injector may not be long enough for i.m. delivery. There are two early studies measuring subcutaneous tissue depth (SCTD). A paediatric study [20] using ultrasound found that 30% of patients weighing greater than 30 kg had an SCTD greater than 1.59 cm, and 12% of patients weighing less than 30 kg had an SCTD greater than the needle length of 1.27 cm. The authors concluded that about one-fifth of the children may not receive an i.m. delivery using a device employing a needle of this length. Another study employed computed tomographic (CT) images of the thigh to measure SCTD. They found a depth for men of 0.66 ± 0.47 cm (range 0.21–3.47) and for women of 1.48 ± 0.72 cm

(range 0.24–3.71). The difference in depth between sexes was statistically significant ($P > 0.0005$). They demonstrated that 2% (1/50) of men and 42% (21/50) of women studied had an SCTD that exceeded 1.43 cm. Therefore, most women and some men would theoretically be at risk of receiving epinephrine subcutaneous rather than i.m. with the use of Epipen [16].

Thus, both of the above-mentioned studies concluded that in some patients, the epinephrine auto-injector needle length was too short for i.m. delivery. But both studies examined the delivery without compression of the thigh. And compression is needed to trigger auto-injectors. This added pressure on the injector produces compression of the subcutaneous tissue by the auto-injector, and the epinephrine delivery depth to the tissue compartment is increased. In order to trigger epinephrine auto-injectors, a certain amount of pressure is needed. For example in the case of Epipen, 2–8 lb. of pressure must be exerted in order to trigger the injector. This can have an effect on the depth of penetration of the needle. There was a study [21] on pig thighs with the use of Epipen. The study showed that the SCTD was 2.78 ± 0.59 cm (range, 2–4 cm). In this study, all epinephrine injections diffused through tissue beyond the auto-injector's needle length of 1.43 cm. The SCTD delivery of epinephrine was 94.4% beyond the length of the auto-injector needle. The force that results in the delivery of epinephrine beyond the subcutaneous fat and into the i.m. tissue is most likely the combination of both the compression of the underlying tissues due to the pressure applied to the injector by the patient and the expulsion pressure produced by the spring-loaded mechanism of the auto-injector. As anaphylaxis provokes a high level of anxiety for a patient or their caregiver, it is likely that even more pressure would be applied thus further increasing the degree of compression. These observations suggest that obese patients may be receiving the medication in the i.m. space in spite of a needle that does penetrate the muscle when simply applied to the thigh.

Subsequently, studies examining the effect of thigh tissue compression on depth of penetration by employing ultrasound were performed. A study [18] in adults found that 36 of 116 (31%) of individuals administered an Epipen experienced a subcutaneous rather than an i.m. delivery of epinephrine. Women were 6.4 times more likely than men to receive epinephrine in the subcutaneous space. Risk factors for subcutaneous injection were short height, higher BMI and thicker thighs. Another study specifically examined patients with food allergy. This study [17] showed that 19 of 100 patients (19%) would not receive epinephrine i.m. when

using an auto-injector. In 28% of female patients, EpiPen needle length is too short for i.m. delivery. Therefore, both studies recommend a longer needle length for epinephrine auto-injections. This has propelled the need for an auto-injector such as Emerade, which has a needle length of 2.5 cm. A longer needle may be helpful in obese patients with higher BMI and thigh circumference.

BARRIER TO USING EPINEPHRINE AUTO-INJECTORS

There are multiple different epinephrine auto-injectors commercially available. They have different ergonomic designs and sizes. There are devices such as Auvi-Q that talks to the patient so that there is less confusion on how to administer the device. Yet, patients still do not carry epinephrine auto-injector or do not use them during anaphylaxis. In a survey of 1385 of patients, the most common reason for failure to use epinephrine was the substitution of an antihistamine, which was done by 38% of respondents [22]. Twenty-eight percent of patients had not received a prescription for epinephrine auto-injector. Other reasons for not using an auto-injector included the perception that the reaction was mild, the substitution of an asthma inhaler, the patient did not have the auto-injector with them or were afraid to inject themselves. Forty-six percent of patients refilled their injector at least once. Refills progressively decreased each year thereafter [23]. For the above reasons, epinephrine may not be given and education about anaphylaxis and avoidance of triggers is critical for patients and caregivers.

Many patients are apprehensive about using an epinephrine auto-injector due to fear of the needle and accidental sticks. Unintentional administration of auto-injectors, typically into thumbs, fingers and hands, remains a problem. Administration into a digit can produce ischemia and potentially gangrene. Multiple treatments have been employed to treat unintentional needle sticks. These include topical nitroglycerin, locally injected terbutaline and locally injected phentolamine to reverse vasoconstriction effects of epinephrine [24]. Other conservative treatments include hot compresses, massage or ice packs. A study [25] of 365 epinephrine hand injections showed that all patients had resolution of their symptoms and none required hand surgeon consultation or surgery.

CONTRAINDICATION FOR USING EPINEPHRINE

There is no absolute contraindication for use of epinephrine during anaphylaxis. Yet, there are

pharmacological concerns for patients taking beta-adrenergic blockers. Beta-adrenergic blockers can increase bronchospasm and decrease cardiac contractility, thus blunting the pharmacologic effects of epinephrine and potentially worsen the event. There is concern that epinephrine may produce dangerous elevations of blood pressure in beta-blocked patients via unopposed alpha adrenergic stimulation and reflex vagotonic effects [26]. In beta-blocked patients failing to respond to epinephrine, glucagon can potentially reverse refractory bronchospasm and hypotension by activating adenylyl cyclase in a non-beta receptor dependent manner [27].

SPECIAL CONSIDERATIONS IN THE ADMINISTRATION OF EPINEPHRINE

Two conditions can complicate the treatment of anaphylaxis with regard to the administration of epinephrine. These are anaphylaxis in the elderly and during pregnancy. Clinicians are cautious about treating anaphylaxis in the elderly population. There is substantial variation in epinephrine-dispensing rates across subsets of the population, ranging from 1.44% for individuals younger than 17 years of age, 0.9% for individuals 17–64 years of age, to 0.32% for those aged 65 years or older [28]. The level of IgE peaks at adolescence and then gradually declines with age. This probably explains the lower incidence of allergies and anaphylaxis in the elderly [29]. But many elderly routinely use medicines that can adversely affect the treatment of anaphylaxis. Beta-blockers are commonly used for hypertension and cardiac protective role but have potentially detrimental physiologic effects as described above. Tricyclic antidepressants decrease the reuptake of catecholamines by neurons and thus interfere with the degradation of epinephrine. This causes elevated levels thus complicating the choice of a 'correct' dose. Monoamine oxidase inhibitors also complicate the use of epinephrine by preventing its degradation. Both angiotensin-converting enzyme inhibitors and angiotensin receptor blockers interfere with the action of angiotensin, which is produced as an endogenous compensatory response to hypotension. In addition, angiotensin-converting enzyme inhibitors prevent the degradation of kinins. Despite all these concerns, there is no absolute contraindication for using epinephrine in anaphylaxis in the elderly.

Management of anaphylaxis in pregnancy is similar to the general population. The use of epinephrine is the same dose as the general population and can be repeated every 5–15 min if necessary [30]. One difference in management is to have the

pregnant woman lie in the left lateral recumbent position to help increase venous flow to the heart.

FUTURE DIRECTIONS IN THE MANAGEMENT OF ANAPHYLAXIS

The recommended administration of epinephrine is by i.m. injection in the lateral thigh (vastus lateralis muscle), but if there is cardiopulmonary arrest during anaphylaxis, high-dose intravenous (i.v.) epinephrine can be administered. One can give 1–3 mg (1:10 000 dilution) i.v. administered over 3 min, and if necessary followed by administering 3–5 mg over 3 min, and still if no response then 4–10 µg/min infusion [14]. Obviously, i.v. administration is only appropriate in a clinic or hospital setting with cardiovascular monitoring available. Epinephrine auto-injectors are recommended for the outpatient setting but underused due to fear of needles and other reasons. There are animal studies of a rapidly disintegrating sublingual epinephrine tablet for treatment of anaphylaxis. This noninvasive administration of epinephrine has shown to be effective due to the high vascularity of sublingual mucosa. Pharmacokinetic studies in rabbits compared 40 mg of sublingual epinephrine with 0.30 mg administered i.m. with EpiPen [31]. Maximum plasma concentration, C_{max} , time to maximum epinephrine concentration, T_{max} and area under the plasma concentration vs. time curve, AUC 0–1 h, were similar. In addition, reducing epinephrine particle size has increased rate and extent of sublingual absorption in rabbits [32]. Further studies in humans may show promising results.

CONCLUSION

Epinephrine is the first line of therapy for patients with anaphylaxis. Yet, it is underused by physicians, patients and caregivers. The failure to administer epinephrine in a timely manner has been associated with fatalities. Better education is crucial in assuring that all patients at risk for anaphylaxis have access to epinephrine auto-injectors and know how and when to use them.

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Dr Song reports as acting as a consultant and speaker for Mylan, Novartis and Teva. Dr Lieberman reports as acting as a consultant and speaker for Mylan.

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