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Who needs to carry an epinephrine autoinjector?

ABSTRACT

Patients who have had anaphylaxis or who are at risk of it (eg, due to food allergy or *Hymenoptera* hypersensitivity) should carry an epinephrine autoinjector at all times. However, the risks and benefits must be considered on an individual basis, especially in patients with atherosclerotic heart disease, elderly patients on polypharmacy, patients receiving allergen immunotherapy, those with large local reactions to insect stings, and individuals with oral allergy syndrome.

KEY POINTS

Based on current data, there is no absolute contraindication to epinephrine for anaphylaxis. And failure to give epinephrine promptly has resulted in deaths.

Clinicians concerned about adverse effects of epinephrine may be reluctant to give it during anaphylaxis.

Education about anaphylaxis and its prompt treatment with epinephrine is critical for patients and their caregivers.

Dr. Song has disclosed membership on advisory committees or review panels for Allergopharma, and teaching and speaking for Novartis and Teva. Dr. Lieberman has disclosed consulting for Kaléo.

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ANAPHYLAXIS IS POTENTIALLY FATAL but can be prevented if the trigger is identified and avoided, and death can be avoided if episodes are treated promptly.

A consensus definition of anaphylaxis has been difficult to achieve, with slight variations among international guidelines. The World Allergy Organization classifies anaphylaxis as immunologic, nonimmunologic, or idiopathic.[1] The National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network highlight clinical symptoms and criteria.[2] The International Consensus on Food Allergy describes reactions as being immunoglobulin E (IgE)-mediated, cell-mediated, or a combination of the 2 mechanisms.[3]

Despite the subtle differences in these definitions, all 3 international organizations have a common recommendation for anaphylaxis: once it is diagnosed, epinephrine is the treatment of choice.

EPINEPHRINE IS THE TREATMENT OF CHOICE FOR ANAPHYLAXIS

Anaphylaxis commonly results from exposure to foods, medications, and *Hymenoptera* venom.[4] Avoiding triggers is key in preventing anaphylaxis but is not always possible.

Although epinephrine is the cornerstone of the emergency treatment of anaphylaxis, many patients instead receive antihistamines and corticosteroids as initial therapy. Some take these medications on their own, and some receive them in emergency departments and outpatient clinics.[5]

Diphenhydramine, a histamine 1 receptor antagonist, is often used as a first-line medication. But diphenhydramine has a slow onset of action, taking 80 minutes after an oral dose

to suppress a histamine-induced cutaneous flare by 50%, and taking 52 minutes with intramuscular administration.[6] Corticosteroids also have a slow onset of action. These drugs cannot prevent death in anaphylaxis, a condition in which the median time to respiratory or cardiac arrest is 30 minutes after ingestion of food, 15 minutes after envenomation, and 5 minutes after iatrogenic reactions.[7]

Combination therapy with diphenhydramine and a histamine 2 receptor antagonist (eg, cimetidine, famotidine) is also commonly used,[8] but this combination offers no advantage in terms of onset of action, and a Cochrane review could find no definitive evidence for or against the use of histamine 2 receptor antagonists.[9]

Because of their slow onset of action, all of these should be second-line therapies, given after epinephrine. Epinephrine is the first line of treatment because it has a maximal pharmacokinetic effect (time to maximal peak serum level) within 10 minutes of intramuscular injection into the thigh.[10,11]

In addition, epinephrine acts on numerous receptors to antagonize the multiple pathologic effects of the mediators released during an anaphylactic episode. In contrast, antihistamines block only 1 mediator, while mediators other than histamine can be responsible for severe events and deaths.[12,13]

It is crucial that epinephrine be given immediately, as delay has been associated with fatalities.[14] In addition, guidelines recommend repeating epinephrine dosing after 5 to 15 minutes if the response to the first dose is suboptimal.[1,2] From 16% to 36% of patients may need a second dose.[15–18] Therefore, many physicians recommend that patients at risk of anaphylaxis keep not 1 but 2 epinephrine autoinjectors on hand at all times, and so say the US guidelines for the management of anaphylaxis.[19]

WHO SHOULD CARRY AN EPINEPHRINE AUTOINJECTOR?

All published guidelines recommend epinephrine as the drug of choice for anaphylaxis. And an epinephrine autoinjector is indicated for anyone who has experienced an anaphylactic event or is at risk of one, and these patients should carry it with them at all times. Such individuals include those with food allergy or *Hymenoptera* hypersensitivity.

Food allergy

The foods that most often cause anaphylaxis are peanuts, tree nuts, fish, shellfish, milk, and eggs, but any food can cause a reaction.

The prevalence of food allergy has increased over time, and treatments are limited. Some food desensitization protocols look promising but are still in the research stages. The best treatment at this time is to avoid the offending food, but there are accidental exposures.

Hymenoptera hypersensitivity

Patients who have had anaphylaxis after being stung by insects such as bees, wasps, yellow-faced hornets, white-faced hornets, yellow jackets, and fire ants should be evaluated by an allergist. Skin testing and serum IgE testing helps properly diagnose *Hymenoptera* hypersensitivity.

Once the diagnosis is confirmed, venom immunotherapy should be considered. Some patients choose only to carry an epinephrine autoinjector and to avoid these insects as much as possible. However, most patients also choose to receive venom immunotherapy, because 80% to 90% of those who receive this treatment for 3 to 5 years do not have a systemic reaction if they are stung again.[20]

Regardless of whether they choose to undergo immunotherapy, sensitive patients should always carry an epinephrine autoinjector. This is also the case after treatment ends, since the therapy is not 100% effective.

Histamine blockers and corticosteroids should be second-line treatments, used after epinephrine

PATIENTS FOR WHOM THE NEED MAY BE LESS CLEAR

In other patients who may be at increased risk, the mandate for an epinephrine autoinjector is less clear, and the decision to carry one is determined on an individual basis. Such individuals are those receiving allergen immunotherapy, with large local reactions to insect stings, with oral allergy syndrome, with mastocytosis, and with drug allergy. In these cases, the benefit vs the burden of carrying an autoinjector should be discussed with the patient.

Patients on allergen immunotherapy

National guidelines recommend that all patients who receive allergen immunotherapy be monitored in the clinic under a physician's supervision for 30 minutes after the injection. Fortunately, life-threatening reactions occurring after 30 minutes are rare. But delayed systemic reactions can occur and may account for up to 50% of such events.[21]

Therefore, many physicians consider it prudent for patients on immunotherapy to carry an epinephrine autoinjector, but there is no consensus. A survey[22] found that 13.5% of allergists did not prescribe the autoinjector for patients on immunotherapy, while 33.3% prescribed it for *all* their patients on immunotherapy, and the rest prescribed based on risk.

Since there are no national guidelines on epinephrine autoinjectors for patients on immunotherapy, the decision should be based on the patient's risks and comorbidities and informed by discussion between the individual patient and his or her allergist.

Patients with large local reactions to insect stings

From 5% to 10% of patients who have large local reactions to insect stings are at risk of systemic reactions.[20]

The foods that most often cause anaphylaxis are peanuts, tree nuts, fish, shellfish, milk, and eggs, but any food can cause a reaction

Patients with oral allergy syndrome

Oral allergy syndrome, also known as pollen-food allergy, causes itching and mild swelling of the mouth, lips, and throat after eating fresh fruits and vegetables. The prevalence ranges from 2% to 10% of patients with allergies.[23]

A survey of allergists found that 20% of patients with oral allergy syndrome had experienced systemic symptoms.[24] The survey also showed that the decision to prescribe an epinephrine autoinjector to these patients was highly variable. Only about 30% of allergists recommend epinephrine autoinjectors to patients with oral allergy syndrome, while most believe that the decision should be based on the individual's symptoms and risk.

More research is needed in the area of food allergy. Because data are limited, there are no national guidelines on whether these patients should carry an epinephrine autoinjector. We agree with the Joint Task Force on Practice Parameters[14] recommendation that the decision be made on an individual basis following discussion between the patient and physician.

Patients with mastocytosis

Patients with mastocytosis and a history of anaphylaxis are at increased risk for systemic reactions to *Hymenoptera* venom.

Patients with medication allergy

Once medication allergy has been diagnosed, avoidance is usually effective, obviating the need for an epinephrine autoinjector, although the physician has the option of prescribing one.

CAUTIONS, NOT CONTRAINDICATIONS

Physicians may be reluctant to prescribe an epinephrine autoinjector because of the risk of an adverse reaction in patients with hypertension, coronary artery disease, or arrhythmias, and in elderly patients taking multiple drugs, especially drugs that can interact with epinephrine. Nevertheless, there is no absolute contraindication to the use of epinephrine in anaphylaxis.

In patients with atherosclerosis and cardiovascular disease

Epinephrine increases vasoconstriction, heart rate, and cardiac force of contraction. These effects are beneficial during anaphylaxis, but in rare cases patients have experienced myocardial infarction and acute coronary syndrome after receiving intravenous epinephrine.[25] These incidents have naturally prompted reluctance to prescribe it in susceptible patients with coronary disease during anaphylaxis.

Yet epinephrine may not be solely to blame for these adverse responses. Mast cells are abundant in the heart, and their release of mediators can also result in adverse cardiac manifestations, including myocardial infarction.[26]

Conversely, some drugs used to treat cardiovascular disease can worsen anaphylaxis.

Beta-blockers can cause bronchospasm and decrease cardiac contractility. They can also blunt the pharmacologic effects of epinephrine. There is concern that epinephrine may produce dangerous elevations of blood pressure in patients taking beta-blockers by unopposed alpha-adrenergic stimulation and

reflex vagotonic effects.[27] And there is evidence that beta-blockers may increase the risk and severity of reactions. One study reported that patients taking beta-blockers are more than 8 times more likely to be hospitalized due to anaphylactoid reaction with bronchospasm.[28]

Beta-blockers and, to a lesser extent, angiotensin-converting enzyme inhibitors have been shown to increase the risk of anaphylaxis in the emergency department.[29,30] However, some investigators have not found beta-blockers to be a risk factor. A study evaluating anaphylactoid reactions from contrast media found no statistically significant higher risk in patients taking beta-blockers.[31] Similarly, a study of 3,178 patients on beta-blockers receiving venom immunotherapy or allergen immunotherapy found no increase in the frequency of systemic reactions.[32] Nevertheless, overall, more studies support the hypothesis that beta-blockers may be an additional risk factor in anaphylaxis.[33]

Thus, clinicians treating patients with cardiovascular disease and anaphylaxis face a dilemma. Although there is concern in this population, epinephrine should not be withheld in patients with cardiovascular disease who are experiencing an anaphylactic event.[33] If epinephrine is not administered, the patient could die.

Elderly patients on multiple medications

Older patients are also at risk of anaphylaxis. But clinicians are reluctant to treat older patients with epinephrine because of concerns about adverse effects.

Epinephrine dispensing rates vary substantially in different age groups: 1.44% for patients under age 17, 0.9% for those ages 17 to 64, and 0.32% for those age 65 or older.[34] A Canadian study of 492 patients with anaphylaxis in the emergency department showed that those over age 50 received epinephrine less often than younger patients (36.1% vs 60.5%).[35] Cardiovascular complications were more frequent in the older group, occurring in 4 (9.1%) of the 44 older patients who received epinephrine compared with 1 (0.4%) of the 225 younger patients who received it. On the other hand, the rate of adverse effects from subcutaneous epinephrine was no different in older asthma patients compared with younger patients.[36]

Many older patients take multiple medications, raising concern about adverse effects. Commonly prescribed medications in the elderly can affect the actions of epinephrine. Monoamine oxidase inhibitors retard the catabolism of epinephrine. Tricyclic antidepressants may decrease the reuptake of catecholamines by neurons and thus interfere with the degradation of epinephrine. Digoxin has a narrow therapeutic window and can potentially increase the risk of arrhythmias when given with epinephrine.

Although the clinician must be cautious in treating older patients who have comorbidities, these are not sufficient to withhold prescribing an epinephrine autoinjector to elderly patients at risk of anaphylaxis.

INJECTOR OPTIONS

Epinephrine autoinjectors come preloaded for prompt delivery of the drug. They are intended primarily for use by patients themselves in unsupervised settings in suspected anaphylaxis. Simplicity of use and safety must be considered in such a setting so that patients can use the device correctly and are not incorrectly dosed.

There is no absolute contraindication to the use of epinephrine in anaphylaxis

Several models are commercially available, with different ergonomic designs and sizes. EpiPen, the first one marketed in the United States, was introduced in 1987. One device (Auvi-Q) contains an audio chip that gives step-by-step instructions at the time of use. It is hoped that this device will reduce errors in usage during this stressful time for patients and caregivers.

In the United States, epinephrine autoinjectors contain either 0.15 or 0.30 mg of the drug, but some clinicians believe this may not be enough. The UK Resuscitation Council recommends 0.50 mg for patients over age 12,[37] and an epinephrine autoinjector with that dose is available in Europe.

Subcutaneous vs intramuscular delivery

The package insert for some epinephrine autoinjectors says the injector can be used to treat anaphylaxis by both subcutaneous and intramuscular administration. However, the routes are not equivalent.

The goal in anaphylaxis is to quickly achieve high tissue and plasma epinephrine concentrations, and studies have found that injection into the vastus lateralis muscle, but not the deltoid muscle, results in faster time to peak plasma concentration: 8 minutes for injection in the vastus lateralis muscle and 34 minutes for subcutaneous delivery.[10,11] In addition, injection in the vastus lateralis muscle results in a higher peak plasma concentration than the subcutaneous or deltoid route. Based on these data, intramuscular injection into the vastus lateralis muscle in the thigh appears to be the preferred route of administration of epinephrine.

Obese patients may need a longer needle

Research on the original autoinjector was conducted by the US military, which wanted a rapidly effective and easy-to-use antidote for battlefield exposure to poison gas. The resulting device had 2 separate spring-loaded syringes, 1 containing pralidoxime chloride and the other atropine sulfate. To enable its use through the thick fabric of a chemical warfare suit, the needles were 2.2 cm long.

The first autoinjector was made for the US military to give an antidote to poison gas

The first commercial autoinjector to contain epinephrine was made by Survival Technology (Bethesda, MD) in the mid-1970s. The manufacturer considered a 2.2-cm needle to be too long, and the first commercially available epinephrine autoinjector, EpiPen, had a 1.43-cm needle for adult use.

Since then, needle lengths have ranged from 1.17 to 2.5 cm to accommodate different skin-to-muscle depths, with shorter needles for children and longer needles for obese adults.[38]

However, the prevalence of obesity is high and continues to rise.[39] Obesity raises concern that the needles in epinephrine autoinjectors may be too short for the preferred intramuscular delivery, resulting in subcutaneous deposition.

A study that used computed tomography of the thigh found that 1 (2%) of 50 men and 21 (42%) of 50 women studied had a subcutaneous tissue depth greater than 1.43 cm, the needle length in EpiPen. These were not anaphylaxis patients, but the findings suggest that many patients—especially women—may be getting subcutaneous instead of intramuscular delivery with this device.[40]

Another study that used ultrasonography showed that the 1.43-cm EpiPen needle was too short for 36 (31%) of 116 adults.[41] Women were 6.4 times more likely than men to encounter this problem. Other risk factors include higher body mass index, short height, and thicker thighs.

Emerade, an injector with a 2.5-cm needle, is available in some European countries. A longer needle may be helpful in some cases. but we do not yet have enough data to determine the optimal needle length.

Conversely, some children may need shorter needles and may in fact be at risk of having the needle penetrate bone.[42] The US Food and Drug Administration recently approved a shorter needle for an epinephrine autoinjector (Auvi-Q) to be used in children weighing 7.5 kg to 15 kg.

BARRIERS TO USING EPINEPHRINE AUTOINJECTORS

Many patients do not use their epinephrine autoinjector in times of anaphylaxis or do not have one with them. Common reasons cited by respondents in a survey[43] of 1,385 patients included the following:

They took an oral antihistamine instead (38%).

They never received a prescription for an epinephrine autoinjector (28%).

They thought their symptoms were mild and would resolve with time (13%).

They were afraid (6%). There are reports of accidental injection, typically into fingers, hands, and thumbs. Fortunately, most accidental injections do not require a hand surgeon evaluation or surgery.[44] Conservative therapy and monitoring of the injection site are sufficient in most cases.

They could not afford an epinephrine autoinjector (1%).[43] Mylan Pharmaceuticals infamously increased the price of its EpiPen to more than $600 for a package of 2 pens. Generic devices are available in the United States but are still too expensive for some patients and are cumbersome to carry.

However, even expensive epinephrine autoinjectors may be cost-effective. Epidemiologic studies have found that patients who did not use an epinephrine autoinjector incurred a

higher burden of cost due to emergency department visits and inpatient hospitalizations.[45]

As a do-it-yourself option, some resourceful patients are obtaining autoinjectors intended for insulin injection, replacing the needle, and filling the injector with epinephrine, at a cost of about $30. (The manufacturer does not endorse this off-label use of their device—www.owenmumford.com/us/patients/if-you-need-to-inject/.) Least costly of all is to prescribe multidose vials of epinephrine and regular syringes and teach patients and their caregivers how to draw up the proper dose and give themselves an injection—in essence going back to what was done before 1987.

It was past its expiration date (2%).[43] Failure to refill the prescription is common. A California Kaiser Permanente study[46] showed that only 46% of patients refilled their epinephrine autoinjector prescription at least once, and the refill rate decreased over time: 43% at 1 to 2 year follow-up, 35% at 3 to 4 years, and 30% at 5 years or longer. Based on these data, it is imperative to educate patients regarding the importance of replacing the epinephrine autoinjector when the old one expires.

NEED FOR PATIENT EDUCATION

Even though prompt treatment with epinephrine decreases fatalities, it continues to be underused in the community. In addition, it is often prescribed without adequate training in its use and appropriate emphasis on the need to keep the device on hand at all times and to replace it in a timely manner if it is used or has expired. Physicians need to educate patients on how to avoid triggers and how to recognize symptoms of anaphylaxis whenever they prescribe an epinephrine autoinjector.

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