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Epinephrine As A Treatment Option For Acute Anaphylaxis – A Review

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Abstract

Anaphylaxis is a multi-system allergic response that can be life-threatening. For the past 30 years, most consensus guidelines have recommended that epinephrine should be used first and foremost in the treatment of acute anaphylaxis. Some state that properly given epinephrine has no absolute contraindication. The data from the medical literature about the proper use of epinephrine for anaphylaxis was assessed by a committee of anaphylaxis experts formed by the World Allergy Organization. The committee is convinced that epinephrine is currently underused and often dosed incorrectly to treat anaphylaxis that it is under prescribed for future self-administration, that most of the reasons proposed to withhold its clinical use are flawed, and that when given in appropriate intramuscular doses, the therapeutic benefits of epinephrine outweigh the risks.

Keywords: Anaphylaxis, Epinephrine, Management, Prevention

Introduction

Most consensus anaphylaxis recommendations published over the past 30 years [1-17] have affirmed that epinephrine is the therapy of choice and the first medicine used for acute anaphylaxis. Clinical pharmacology research, clinical observation, and animal models are used to make therapeutic recommendations for epinephrine administration in anaphylaxis. Anaphylaxis can be happen after eating something or being stung by a bug, and it can happen suddenly and without warning. Even though the stimulus is the same, the severity changes from episode to episode in the same patient. For health care professionals and others without medical expertise, recognizing and diagnosing anaphylaxis can be challenging [18]. Because of the nature of the condition, there have been few controlled clinical studies and no placebo-controlled trials in anaphylaxis. Because of the overwhelming body of evidence suggesting that prompt epinephrine administration is optimum, if not vital, for survival in many cases [20-25], randomizing to a non-epinephrine treatment would be unethical. In this review, we study the current evidences for epinephrine's usage in anaphylaxis.

Anaphylaxis

Traditional anaphylaxis terminology uses the word anaphylactic to describe IgE-dependent responses and anaphylactoid to describe IgE-independent reactions, which are clinically identical. This terminology should be replaced with immunologic (IgE-mediated and non-IgE-mediated [eg, IgG and immune complex complement-mediated]) and nonimmunologic anaphylaxis, according to the

World Allergy Organization, a global federation of national and regional allergy and clinical immunology societies and organisations dedicated to raising awareness and advancing excellence in clinical care, education, research, and training in allergy and clinical immunology. As a result, the word anaphylaxis in this article refers to both immunologic and nonimmunologic anaphylaxis.

Anaphylaxis in Perspective

Anaphylaxis is an abrupt and possibly fatal multi-system allergic reaction characterised by generalised erythema, pruritus, angioedema, bronchospasm, laryngeal edema, hypotension, cardiac arrhythmias, sense of impending doom, unconsciousness and shock. Itchy nose, eyes, throat, genitalia, palms, and soles; rhinorrhea; change in voice; metallic taste; nausea, vomiting, diarrhoea, stomach cramps, and bloating; lightheadedness; headache; uterine cramps; and widespread warmth are some of the other early or contemporaneous signs and symptoms of anaphylaxis. In 2004 and 2005, the US National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network hosted symposia in which an international and interdisciplinary group of representatives and experts from 16 professional, government, and lay organizations attempted, among other things, to establish clinical criteria that would improve anaphylaxis diagnostic precision [16]. Anaphylaxis is likely to be present clinically if any one of three criteria is met between minutes to hours, according to the researchers:

(1) Acute onset of illness with skin, mucosal surface, or both involvement and at least one of the following: respiratory compromise, hypotension, or end-organ dysfunction;

(2) Two or more of the following occur rapidly after exposure to a likely allergen: involvement of skin or mucosal surface, respiratory compromise, hypotension, or persistent gastrointestinal symptoms; and

(3) Hypotension develops after exposure to a known allergen for that patient: age-specific low blood pressure [16].

"These criteria are expected to capture more than 95 percent of instances of anaphylaxis," according to a study [27]. This study data suggest that more than merely cutaneous as well as less severe symptoms must exist before the administration of epinephrine. Anaphylaxis might start off mildly and quickly escalate into a life-threatening respiratory and cardiovascular response. Delaying therapy until the beginning of multiorgan symptoms, as recommended by the Anaphylaxis Working Group report's clinical criteria for diagnosis, may be dangerous because the eventual severity of anaphylaxis is difficult or impossible to anticipate at the time of commencement. As a result, some authors and members of the World Allergy Organization's Ad Hoc Committee on Epinephrine and Anaphylaxis recommend that any symptoms of anaphylaxis, such as generalized pruritus, erythema, urticaria, and angioedema alone, as well as any other systemic symptom not involving vital organs, should be treated immediately and as needed with appropriate intramuscular doses of epinephrine in an attempt to prevent more severe anaphylaxis from occurring. Symptoms clearly attributable to another diagnosis with a much higher clinical probability, such as generalised pruritus, urticaria, and angioedema associated with new-onset acute urticaria and angioedema, or an exacerbation of chronic urticaria and angioedema, do not require epinephrine treatment. As a result, there are two groups of thought as to when injectable (intramuscular) epinephrine should be given for anaphylaxis or what appear to be early signs of anaphylaxis. One group believes that epinephrine should be given as directed by the US National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network [16], while another group believes that epinephrine should be given as soon as possible after the onset of the least serious or minor symptoms, especially when the offending agent or allergen is administered parenterally. Parenteral administration of the offending allergen or causative agent is linked to faster absorption and potentially fatal anaphylaxis than oral administration, according to research. However, anaphylaxis can be caused by any route of administration, oral or parenteral, and might start with modest symptoms and progress to anaphylactic mortality. The most frequent inciting causes for anaphylaxis include foods, drugs, insect stings, and allergy immunotherapy injections, although it can be triggered by any substance capable of causing a quick degranulation of mast cells or basophils [28]. In

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clinical practice, anaphylaxis triggered by diagnostic and therapeutic procedures is practically unavoidable and happens in a range of clinical scenarios [16]. The lifetime individual risk of anaphylaxis is estimated to be 1% to 3%, with a 1% death rate and the prevalence of anaphylaxis may be on the rise [28, 29]. As a result, all doctors must be able to diagnose anaphylaxis, treat it effectively, and give advice on how to avoid it in the future. Anaphylaxis manifests itself in a variety of ways, but the most prevalent are cutaneous manifestations (generalised erythema, pruritus, urticaria and angioedema) [28]. The commencement of reactions may be quick and uniphasic or they can be delayed, biphasic (recurrent), or prolonged. Biphasic anaphylaxis occurs in 1% to 20% of anaphylaxis cases, and symptoms can reoccur 1 hour to 72 hours (often within 8 hours) after the first phase appears to have resolved [30]. Although failing to administer a sufficient amount of epinephrine early in an anaphylactic response may be related with an increased risk of biphasic anaphylaxis, the intensity of the initial phase of an anaphylactic reaction is not predictive of either biphasic or prolonged anaphylaxis. In more severe cases, patients may need to be monitored for 24 hours or longer after they appear to have recovered from the initial phase, because life-threatening anaphylaxis symptoms may recur. The number of times two or more doses of epinephrine are required to treat anaphylaxis is unknown (studies range from 16 to 36 percent), and numerous cofactors may be involved [31-33]. The most common causes of death are respiratory compromise and cardiovascular collapse [28, 34]. An analysis of 202 anaphylaxis fatalities in the United Kingdom from 1992 to 2001 found that the time between the onset of food anaphylaxis symptoms and fatal cardiopulmonary arrest was 25 to 35 minutes on average, which was longer than the time between the onset of insect stings (10-15 minutes) or drug toxicity (mean, 5 minutes in hospital; 10-20 minutes prehospital) [34]. During anaphylaxis, increased vascular permeability can move up to 35% of intravascular fluid to the extravascular space within 10 minutes [35]. The intrinsic compensatory response to anaphylaxis (endogenous epinephrine and other catecholamines, as well as angiotensin II, endothelin-1, and others) influences the severity of clinical manifestations and, when adequate, can save lives without medical intervention, which can lead to diagnostic and therapeutic confusion. Some researchers believe that anaphylaxis might induce myocardial ischemia by encouraging plaque rupture because mast cells aggregate at the locations of coronary atherosclerotic plaques and IgE antibodies linked to mast cells can activate mast cell degranulation. Coronary artery vasospasm can also be caused by stimulation of the H1 histamine receptor [37, 38].

Pharmacological Actions of Epinephrine

The α-adrenergic vasoconstrictive actions reverse peripheral vasodilation, alleviating hypotension and reducing erythema, urticaria, and angioedema at appropriate doses and routes of administration. Antigen absorption from a sting or injection may be reduced by injecting epinephrine locally. Epinephrine's β-adrenergic characteristics produce bronchodilation, enhance myocardial output and contractility, and stop mast cells and basophils from releasing more mediators [41, 42]. Low doses of epinephrine (e.g., 0.1μg/kg) have been shown to cause vasodilation, hypotension, and an increase in the production of inflammatory mediators [39, 43]. The use of epinephrine improves coronary blood flow. An increased length of diastole relative to systole and a vasodilator effect induced by enhanced myocardial contractility are most likely to blame. These responses normally counteract epinephrine's vasoconstrictor effects on the coronary arteries [39, 44]. Because retrospective human studies show that prolonged dosing is linked with poor outcomes [20, 21], achieving peak plasma and tissue epinephrine levels quickly appears to optimise survival. However, administering epinephrine during anaphylaxis is not always successful, and patients may die [20-25]. Delay in administration, inadequate doses, inappropriate route of administration, use of expired epinephrine, resulting in inadvertent administration of an inadequate dose, or an underlying disease, such as poorly controlled asthma, cardiovascular disease, mastocytosis, and possibly other serious systemic disorders [40, 45]. A research in a canine model also shown that delaying epinephrine treatment until hypotension has occurred reduces the effectiveness of reaching peak epinephrine plasma levels and hemodynamic recovery [46]. Epinephrine has a small therapeutic window. Agitation, anxiety, tremulousness, headache, dizziness, pallor, or

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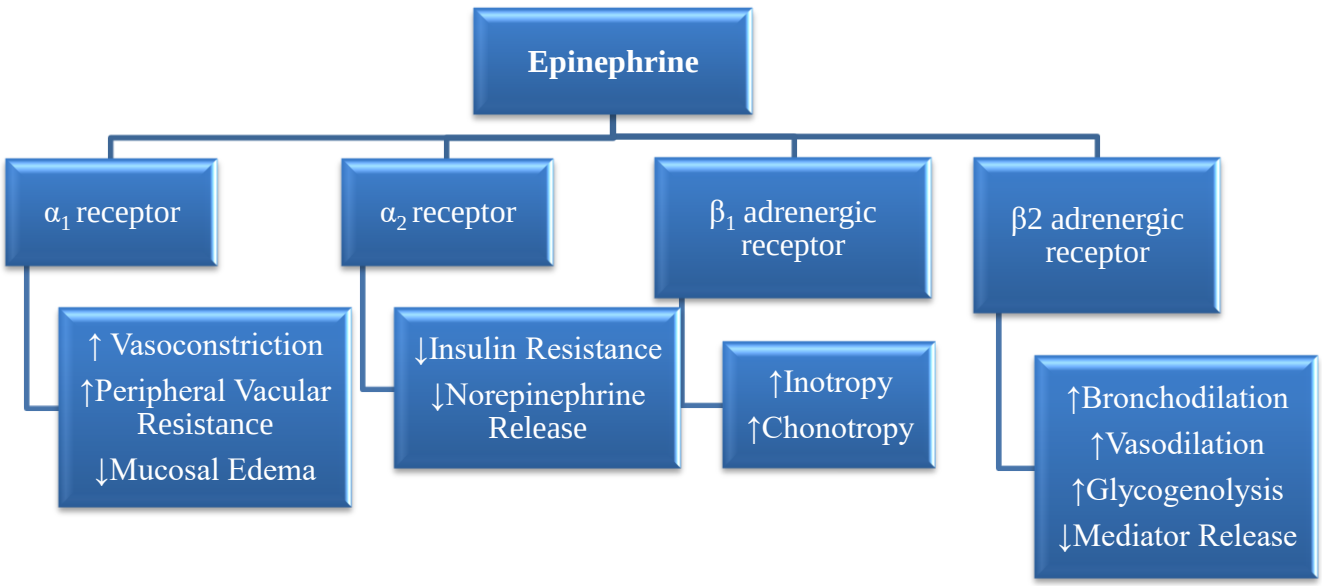
palpitations are all common pharmacological effects that can occur at acceptable levels by any route of administration. In adults and children, epinephrine administration may contribute to or cause myocardial ischemia or infarction, [47-52] pulmonary edema, [53, 54] prolonged QTc (QTc = QT interval divided by the square root of the RR interval [in seconds] of the electrocardiogram) interval, [55] ventricular arrhythmias, accelerated hypertension, and intracranial hemorrhage in adults and children [41, 56]. Despite this, several individuals have survived enormous epinephrine overdoses with no signs of cardiac ischemia [57, 58]. Individuals with hypertension, peripheral vascular disease, ischemic heart disease, or untreated hyperthyroidism (increased number of β-adrenergic receptors in the vasculature of these individuals render the myocardium more sensitive to β-adrenergic effects of epinephrine) [59]. Drug interactions may potentially raise the risk of harmful effects with some medications [13, 18, 42, 59]. Some medications reduce the effectiveness of endogenous catecholamine stores or exogenously administered epinephrine (β-adrenergic blockers), interfere with intrinsic compensatory responses to hypotension (angiotensin-converting enzyme inhibitors and possibly angiotensin II receptor blockers), or obstruct epinephrine metabolism, resulting in increased plasma and tissue concentrations (tricyclic antidepressants and monoamine oxidase inhibitors). The β-adrenergic antagonists and α-adrenergic antagonists can also potentially exaggerate pharmacological effects of epinephrine by permitting unopposed α-adrenergic (vasoconstrictor) and β-adrenergic (vasodilator) effects, respectively. Cocaine and amphetamines sensitize the myocardium to effects of epinephrine, thus increasing the risk of toxicity. However, none of these factors are absolute contraindications to administering epinephrine for anaphylaxis [13].

Fig 1 Shows Adrenergic Effects of Epinephrine



Management of Anaphylaxis

The following basic therapeutic agents should be available to physicians and other health care providers who conduct operations or deliver drugs to treat anaphylaxis [4, 7, 13] -

(1) Stethoscope and sphygmomanometer;

(2) Tourniquets, syringes, hypodermic needles, large-bore needles (eg, 14- or 16-gauge);

(3) Injectable aqueous epinephrine 1:1000 (1 mg in 1 mL; physicians are being urged to express doses in

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mass concentration, eg, 1 mg in mL, rather than as ratios, eg, 1:1000, which have been identified as a source of dosing errors with epinephrine and other medications);

(4) Equipment and supplies for administering supplemental oxygen;

(5) Equipment and supplies for administering intravenous fluids;

(6) Oral or laryngeal mask airway;

(7) Diphenhydramine or similar injectable antihistamine;

(8) Ranitidine or other injectable H2 antihistamine;

(9) Corticosteroids for intravenous injection; and

(10) Vasopressors (eg, dopamine or norepinephrine)

Other items that some physicians could find useful, depending on the clinical situation [13], include glucagon, an automated defibrillator, and a 1-way valve face mask with oxygen inlet port.

Before moving on to subsequent management stages, assessment and maintenance of airway, breathing, circulation are needed. Patients are continually followed in order to discover any clinical changes or therapeutic problems as soon as possible. Placing a patient in the recumbent position with elevation of the lower extremities is strongly suggested because care in the sitting or upright position has linked to poor results in some patients [34].

Epinephrine Administration

Epinephrine should be given at the same time as the other measures [12-14]. There is no definitive contraindication to epinephrine treatment in anaphylaxis, according to professional opinion based on anecdotal evidence [13]. Regardless of the first signs and symptoms of anaphylaxis, it can be given in dosages adequate for the severity of the response. The first reaction to epinephrine determines all future treatment actions. The emergence of toxicity or an insufficient response to epinephrine injections indicates the need for other therapy modalities [13].

Management of Acute Anaphylaxis

I. Immediate intervention -

a. Assessment of airway, breathing, circulation, and adequacy of mentation

b. Administer epinephrine intramuscularly every 5 to 15 minutes, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms, such as respiratory distress, hypotension, shock, and unconsciousness.

II. Possibly appropriate subsequent measures depending on response to epinephrine -

a. Place patient in recumbent position and elevate lower extremities

b. Establish and maintain airway

c. Administer oxygen

d. Establish venous access

e. Isotonic sodium chloride solution intravenously for fluid replacement

III. Specific measures to consider after epinephrine injections, where appropriate

a. Consider epinephrine infusion

b. Consider H1 and H2 antihistamines

c. Consider nebulized β2 agonist (eg, albuterol [salbutamol]) for bronchospasm resistant to epinephrine

d. Consider systemic corticosteroids

e. Consider vasopressor (eg, dopamine)

f. Consider glucagon for patient taking β-blocker

g. Consider atropine for symptomatic bradycardia

h. Consider transportation to an emergency department or an intensive care facility

i. For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary (see reference for specific details)

Epinephrine Injections

According to expert consensus and anecdotal evidence, aqueous epinephrine 1:1000 dilution (1 mg in 1 mL), 0.2 to 0.5 mg (0.01 mg/kg in children; maximum dose, 0.3 mg) administered

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intramuscularly every 5 to 15 minutes or as needed, depending on the severity of the anaphylaxis, should be used to control symptoms and maintain or increase blood pressure [12-14]. Efficacy comparisons of intramuscular and subcutaneous injections during acute anaphylaxis have not been done. In asymptomatic adults and children who get epinephrine intramuscularly in the anterolateral thigh (vastus lateralis), however, absorption is complete and quick, and plasma levels are higher [60, 61]. The thickness of the subcutaneous fat pad in overweight and obese people may prevent intramuscular access [62-64]. Epinephrine autoinjectors are now available in two fixed doses: 0.15 mg and 0.3 mg. They are simple to use and inject through clothes. Overdosage in babies getting 0.15 mg, overdosage in certain small children receiving 0.3 mg, and underdosage in many teenagers receiving 0.15 mg are all possibilities [17, 40]. Although the relative benefits and risks of dosage may vary depending on the individual, autoinjectors containing 0.15 mg of epinephrine are recommended for otherwise healthy children weighing 10 to 25 kg (22-55 lb), and autoinjectors containing 0.3 mg of epinephrine are recommended for children weighing 25 kg (55 lb) or more [17, 40].

Intravenous Epinephrine

During cardiac arrest or in unresponsive or severely hypotensive patients who have failed to react to intravenous volume replacement and several epinephrine injections, epinephrine should be delivered via infusion [13]. When the rate is titrated to clinical response, one group of investigators claims that intravenous epinephrine is safe, efficacious, and well tolerated, however this has not been investigated systematically in a cohort trial comparing this modality to epinephrine intramuscular injections [67].

Inhaled Epinephrine

Some doctors propose inhaling epinephrine instead of injecting it during anaphylaxis, but it has dose-limiting side effects include perioral paresthesias, unpleasant taste, and gastrointestinal symptoms, and it may not generate rapid substantial increases in plasma epinephrine concentrations [68, 69]. There have been no direct comparisons between the inhaled and intramuscular methods of epinephrine delivery.

Follow-Up and Observation after Anaphylaxis

Because there are no accurate predictors of biphasic anaphylaxis, observation times should be tailored and depending on such criteria as comorbid disorders and distance from the patient's house to the nearest emergency centre. After the acute episode has passed, patients should be given an epinephrine autoinjector and thoroughly taught on how to use it in the event of a future incident. They should be given an Anaphylaxis Emergency Action Plan that is tailored to them [18]. Patients should also have immediate access to emergency medical services so that they may be transported to the nearest emergency department (ED) for treatment after receiving the extra epinephrine injection.

Use of Epinephrine by Health Care Professionals

Despite the fact that several anaphylactic recommendations have been established, doctors and other health care workers frequently fail to follow them. For example, according to the UK Resuscitation Council guidelines on anaphylaxis, only 4 (5 percent) of 78 senior house officers beginning ED responsibilities in the United Kingdom would administer epinephrine appropriately, with the proper dose and route of administration, as outlined in the questionnaire. Other studies looked at treatment practices in EDs of civilian [71] and military [72] hospitals in the United States and found that epinephrine injections were given in 16 percent to 50 percent of patients, respectively, during acute anaphylaxis, as suggested by consensus anaphylaxis recommendations. Based on International Classification of Diseases, Ninth Revision, Clinical Modification coding, a retrospective review of a national reporting database on ED visits in the United States from 1993 to 2004 indicated 12.4 million allergy-related ED visits, or about 1% of all ED visits. Anaphylaxis coding was uncommon (0.01 percent of all ED visits), but epinephrine was given to 50 percent of those who were categorized as having anaphylaxis. Epinephrine administration was uncommon (11%) in patients with acute allergy symptoms, and the trend of usage decreased from 19% to 7% (P = 0.04) across the study period [73].

Similar knowledge gaps in primary care providers' awareness of anaphylaxis have been discovered. In a random sample of 468 doctors in the United States, for example, a questionnaire based on the clinical situation of a kid with peanut-induced anaphylaxis

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was employed. About half of those polled (56 percent) believed that the situation simulated anaphylaxis and that epinephrine therapy was necessary. The majority (81 percent) made the proper decision to send the kid home with self-injectable epinephrine and either refer the child to an allergist or prescribe additional diagnostic testing (86 percent). Other countries have conducted similar investigations (several studies are cited in Pongracic and Kim [75]).

Many health care providers are also unsure how to use an epinephrine autoinjector, according to studies [76, 77]. As a result, they are unable to appropriately train their patients. Available materials might assist clinicians in developing treatment regimens and resolving therapeutic conundrums [17, 18, 65].

Under utilization of Epinephrine by Patients, Parents, and Caregivers

The majority of fatalities during witnessing anaphylaxis occurs outside of a medical facility and is caused by delayed epinephrine treatment. All subjects who survived epinephrine before or within 5 minutes of developing severe respiratory symptoms in a retrospective review of 6 fatal and 7 nonfatal episodes of food-induced anaphylaxis in children and adolescents had received it before or within 5 minutes of developing severe respiratory symptoms. Before the commencement of severe respiratory symptoms, none of the participants with fatal episodes received epinephrine [20]. According to statistics from a nationwide case registry of fatal food anaphylaxis in the United States, only a small percentage of people (7/63) had access to epinephrine autoinjectors at the time of death [23, 25]. Pumphrey [21] found that while epinephrine was provided in 62 percent of fatal allergic responses in the United Kingdom that he looked at, it was only delivered in 14 percent of those cases before cardiac arrest. Pumphrey and Gowland [24] reported that 19 (40 percent) of the 48 cases of fatal food anaphylaxis received epinephrine autoinjectors, but more than half of the fatalities occurred in patients whose previous clinical reactions were so mild that a physician would not have prescribed a precautionary epinephrine syringe, in the opinion of the investigators.

The absence of accessible epinephrine for injection during anaphylaxis that occurs outside of a medical facility might be due to a variety of circumstances. According to a worldwide study performed under the auspices of the World Allergy Organization, epinephrine autoinjectors were accessible in roughly half of the nations examined, and the cost of an autoinjector in certain countries was similar to the typical citizen's monthly salary [78]. Autoinjectors with 0.15-mg and 0.3-mg dosages were accessible in 17 (44%) and 22 (56%) of the 39 countries, respectively.

Another problem is adherence to an action plan that includes keeping epinephrine on hand at all times and injecting it during anaphylaxis. Kemp and colleagues [79] found that 32 (47 percent) of 68 patients did not have the required epinephrine autoinjector with them when they developed anaphylaxis from a previously diagnosed cause in a follow-up study. In contrast, 31 (91%) of 34 patients with idiopathic anaphylaxis (i.e., no identifiable cause) had epinephrine on hand at the time of a second episode. Over the next ten years, an instructional procedure emphasizing the need of carrying epinephrine raised the frequency of adherence from 53 percent to 92 percent [80]. According to other research, 50 percent to 75 percent of patients who have been prescribed epinephrine carry it with them, with 30 percent to 40 percent of those able to demonstrate correct delivery technique [81-84]. Others have epinephrine on hand but choose not to use it in the event of anaphylaxis [32, 85-87] or choose to seek emergency medical help [21].

Few studies have looked at anaphylaxis management in schools or daycare settings [75]. An interdisciplinary strategy is required to protect children at risk of anaphylaxis in school, day care, or other settings [9].

Precautions for the Patient at Risk for Anaphylaxis

Because subsequent anaphylaxis may be deadly despite good therapy, optimising prevention is critical. If an allergist-immunologist is not already engaged in the anaphylaxis plan of treatment, he or she can give detailed expert guidance on these issues. All patients who are at risk of anaphylaxis should have at least one epinephrine syringe on hand and know how to use it.

Conclusions

The benefit of taking proper amounts of injectable epinephrine in anaphylaxis substantially outweighs

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the danger, according to existing data (evidence category IV). Because fatalities in anaphylaxis frequently arise from delayed or insufficient epinephrine delivery, consensus opinion and anecdotal evidence urge administering epinephrine "sooner rather than later," that is, when the early signs and symptoms of anaphylaxis occur, regardless of severity. Experts may disagree on how to identify and manage anaphylaxis based on a clinical threshold. They do agree, however, that once the threshold is crossed, suitable amounts of intramuscular epinephrine should be provided quickly. In anaphylaxis, there is no definite contraindication to epinephrine delivery, and all subsequent therapeutic actions are dependent on the first epinephrine reaction. The emergence of toxicity or an insufficient response to epinephrine injections indicates the need for other treatment approaches. All people who are at a higher risk of anaphylaxis should have an anaphylactic action plan and carry epinephrine autoinjectors. Individuals in this situation (and their care givers, if applicable) should be evaluated on a regular basis for compliance with these instructions and the ability to show adequate epinephrine administration technique using a placebo device.

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