ADRENALINE AUTOINJECTOR IN ANAPHYLAXIS: AN AWARENESS UPDATE

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Abstract

Background: Anaphylaxis is a potentially life-threatening allergic type 1 immediate hypersensitivity reaction mediated by IgE antibody. Anaphylaxis is an acute medical emergency and should be treated promptly as it can prove to be fatal. Time interval between the onset of symptoms and rapidity of intervention is a crucial determinant in the treatment of fatal anaphylaxis. Adrenaline injected by an auto-injector into the anterolateral aspect of the thigh is the gold standard of care in the management of acute anaphylaxis. Inspite of the fact that adrenaline is an established therapy for treatment of acute anaphylaxis, the use of adrenaline auto-injectors in severe reactions, is still much restricted. The core concept of significance and awareness of first responder management of anaphylaxis with adrenaline auto-injectors along with therapeutic patient education among Indian population is still in its preliminary stages in addition to fears over safety and prescription.

Objective: This review article focuses on the fact that Adrenaline is the gold standard therapy for anaphylaxis and timely intervention with the appropriate preparation of adrenaline can be life saving. It also focuses on the need for creating an awareness and that widespread use of appropriate prescription strategies by a coordinating expert panel of health care professionals along with patient educational guidelines can to a great extent improve patient outcome in acute anaphylaxis.

Conclusions: There is a strong and urgent need for a coordinating expert panel of concerned health care professionals for framing a geographical variation oriented anaphylactic treatment plan for appropriate use of adrenaline and an appropriate device modification strategy to suit the population along with patient educational guidelines. This to a great extent can improve patient outcome measures in acute anaphylaxis.

Key-words: Adrenaline autoinjectors, anaphylaxis, emergency, timely intervention, life saving, expert panel, guidelines on prescribing, awareness.

Introduction

Anaphylaxis is “a serious, life-threatening generalized or systemic hypersensitivity reaction” and “a serious allergic reaction that is rapid in onset and might cause death”1. The world allergy organization has proposed that anaphylaxis is likely to be present clinically if any one of following three criteria is satisfied within minutes to hours: (i) acute onset of illness with involvement of skin, mucosal surface, or both, and at least one of the following: respiratory compromise, hypotension, or end-organ dysfunction; (ii) 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 (iii) hypotension develops after exposure to a known allergen for that patient: age-specific low blood pressure or decline of systolic blood pressure of >30% compared to baseline.

Anaphylaxis is used to describe rapid onset, and often unpredictable immunologically mediated event that can occur after exposure to a foreign substance in previously sensitized patients. The term ‘anaphylaxis’ is derived from the Greek word ‘ana’ meaning backward and ‘phylaxis’ mean protection.

Epidemiology

The prevalence of anaphylaxis is estimated to be as high as 2%, and appears to be rising, particularly in the younger age group2. The true global incidence of anaphylaxis due to various triggering factors is unknown, because of under-reporting by patients, family members and also due to the failure of diagnosis by healthcare professionals and other paramedical staff. Lifetime prevalence based on international studies is estimated to be 0.05-2%3.

Etiopathogenesis and clinical presentation: It is a systemic IgE-mediated immediate hypersensitivity reaction resulting from the sudden release of multiple mediators from mast cells and basophils. It involves immediate release of several vasoactive amines the most important being histamine in addition to other mediators from mast cells followed by recruitment of inflammatory cells.

Foods are the most common triggers of anaphylactic reactions, followed by drugs, insect stings and chemicals along...
with foreign proteins and idiopathic anaphylaxis is also known to occur.

Table 1 shows the common triggers of anaphylaxis.

<table>
<thead>
<tr>
<th>No</th>
<th>Triggers</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Food Products</td>
<td>Milk, Egg, Peanut, Tree Nuts, Fish, Soy products</td>
</tr>
<tr>
<td>2</td>
<td>Drugs, Chemicals &amp; foreign Proteins</td>
<td>Penicillin, Cephalosporins, Anti TB, Aspirin and other NSAIDs, Opioid Analgesics, ACE inhibitors, IV Iron, Anti Cancer Agents, Monoclonal Antibodies, Intravenous contrast media, Blood Products and Intravenous Fluids (Colloidal Starch), Protamine and Chlorella, Vaccines and Antisera, Medical Dyes such as Fluoroscein, Latex.</td>
</tr>
<tr>
<td>3</td>
<td>Contaminants in medications</td>
<td>Over Sulphated Chondrin sulphate in Heparin</td>
</tr>
<tr>
<td>4</td>
<td>Insect stings</td>
<td>Bees, Wasps, Scorpion, Reptiles</td>
</tr>
<tr>
<td>5</td>
<td>Allergen Skin test/ Provocation tests</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Idiopathic (upto 20%)</td>
<td></td>
</tr>
</tbody>
</table>

The clinical manifestations may be local or systemic and range from mild rhinitis to fatal anaphylaxis. Systemic anaphylaxis is characterized by vasodilatation leading to flushing, urticaria, hypotension and a reduced level of consciousness, increased capillary permeability leading on to angioedema and laryngeal oedema, activation of vagal pathways leading to bradycardia and neurocardiogenic syncpe.

**Diagnosis & treatment**

The diagnosis of anaphylaxis is based primarily on clinical signs and symptoms, as well as a detailed description of the acute episode, including antecedent activities and events.

Adrenaline is the mainstay of treatment and drug of choice for anaphylaxis and should be given immediately to any patient with a suspected anaphylactic episode. Adrenaline is the first drug administered for acute anaphylaxis, as confirmed internationally by the consensus anaphylaxis guidelines published in the English language over the past 30 years.

**Pharmacology of adrenaline:**

Adrenaline is a nonselective directly acting sympathomimetic drug having action on all the adrenergic receptor types namely α1, α2, β1, β2 and β3 receptors. It is one of the most potent vasopressor drugs known and a powerful cardiac stimulant. The rapid rise in blood pressure that occurs after adrenaline administration is due to the direct myocardial stimulant action that produces a positive inotropic and a positive chronotropic effect on the heart and the vasoconstriction induced in many vascular beds.

Its beta adrenergic receptor activity is responsible for the increase in force of myocardial contraction, the powerful bronchodilator dilator action and the suppression of histamine and leukotriene release.

Stimulation of Beta-2 adrenergic receptors located on mast cells inhibit antigen induced release of inflammatory mediators and thus early adrenaline can attenuate the severity of IgE-mediated allergic reactions. Therefore prompt adrenaline can reverse the peripheral vasodilatation, bronchospasm and can reduce the oedema in anaphylactic shock.

Adrenaline helps in alleviating pruritus, urticaria and angioedema of anaphylaxis in addition to its beneficial effects on the gastrointestinal and genitourinary symptoms due to its smooth muscle relaxant effect on intestine and bladder.

Adverse effects: Adverse effects are rare when administered in correct doses through intramuscular injection.

Adrenaline injection can cause transient and moderate anxiety, sweating, apprehension, restlessness, tremor, dizziness, palpitations; pallor, nausea and vomiting, headache, and respiratory difficulty in some patients receiving therapeutic doses of epinephrine, but these effects are more common in patients with preexisting hypertension or hyperthyroidism. Large doses can cause acute hypertension.

Cardiac arrhythmias, including fatal ventricular fibrillation, can occur especially in patients with underlying heart disease or in those receiving interacting drugs. Even incidences of cerebral hemorrhage due to rapid rise in blood pressure, particularly in elderly patients with cardiovascular disease can occur. Angina may occur in patients with coronary artery disease. The potential for adrenaline to produce these types of adverse reactions does not contraindicate its use in an acute, life-threatening allergic reaction.

Adrenaline should be administered simultaneously with other supportive measures. By expert consensus based on anecdotal evidence, there is no absolute contraindication to adrenaline administration in anaphylaxis.
Table 2 shows the stepwise management of anaphylaxis in a clinical care setting.

1. Prevention of further contact with allergen

2. The patient should be placed in a comfortable position. Patients with airway or breathing problems prefer to sit, while a hypotensive patient should be made to lie flat, with or without foot end elevation

3. Airway patency must be maintained

4. Cardio Pulmonary Resuscitation should be carried out if necessary

5. Prompt Administration of intramuscular Adrenaline: 1:1000 solution i.0.3 - 0.5 mL (0.5 milligram) in adults.
   ii.Above 12 years: 500 micrograms IM (0.5 mL)
   i.e. same as adult dose
   iii.300 micrograms (0.3 mL) if child is small or prepubertal
   iv. Above 6 to 12 years: 300 micrograms IM (0.3 mL)
   v. Above 6 months to 6 years: 150 micrograms IM (0.15 mL)
   vi. Less than 6 months: 150 micrograms IM (0.15 mL)

6. Administration of antihistamines: Inj. Chlorpheniramine 10 mg intramuscularly or slow IV

7. Administration of corticosteroids: Inj. Hydrocortisone sod. succinate 200 mg IV

8. Supportive treatment includes: Nebulised β2 Agonists like Salbutamol, IV Fluids and high flow Oxygen

Adrenaline auto-injectors

In the 1960s, after publication of several case series involving people in community settings with anaphylaxis triggered by foods, medications, and stinging insect venoms, syringes prefilled with adrenaline were introduced so that in the absence of a healthcare professional, those without medical training could inject adrenaline readily. In 1980, adrenaline auto-injectors were introduced. The auto-injector technology currently employed for self-injectable adrenaline devices was originally developed for military personnel and was designed to ensure the rapid and reliable delivery of potentially life-saving medication in time-sensitive, high-stress battlefield situations. The patients with a known history of anaphylactic reactions are candidates for specialist care and opinion. Identification of the triggering factors together with avoidance of the triggers in addition to a standard anaphylactic therapeutic strategy, immunotherapeutic measures and patient education are the keystones in the management of a patient with a known history of anaphylactic reaction.

The median time to cardiac or respiratory arrest is about 30 minutes for food allergens, 15 minutes for insect venom and 5 minutes for medications or radiological contrast reagents. Etiological factor is important to decide rapidity of treatment and to prevent future episodes. Therefore, prompt diagnosis of the episode and timely management of the condition is imperative. Delay in administration of adrenaline is a known risk factor for food allergy related mortality. Anaphylaxis is an acute medical emergency and, it can prove to be fatal and time of intervention is crucial and it requires immediate drug administration for reducing the morbidity and mortality. Autoinjectors are very useful and handy devices for the rapid administration of the recommended drugs immediately during the critical hour of need. They are ideal for emergency situations, for mass casualty management, have fast onset of action and can be self administered by the patients themselves or by a first responder. First responder management with adrenaline auto-injector can be life saving in situations where medical help cannot be sought immediately.

The term ‘first responder’ refers to the individual who initially recognises and initiates the treatment for anaphylaxis, for example, the individuals themselves, family members and community nurses.

Indication:
Adrenaline auto-injector is indicated for patients at increased risk of an idiopathic anaphylactic reaction, or for any patient with existing high risk of an allergic reaction to triggers such as venom stings and food-induced reactions. An auto-injector is not usually needed for patients who are known for drug-induced anaphylaxis, until otherwise it is difficult to avoid the drug.

Ideally, all patients should be assessed by an allergy specialist and have a treatment plan based on their individual risk. Healthcare professionals should be familiar with the use of the most commonly available auto-injector devices. If an adrenaline auto-injector is the only available adrenaline preparation when treating anaphylaxis, healthcare providers should use it according to the UK resuscitation council guidelines. Individuals provided with an auto-injector on discharge from hospital must be given instructions and training and should have appropriate follow-up including contact with the patient’s general practitioner.

Device and Dose:
Adrenaline is available in prefilled syringes containing a predetermined dose that can administered by
means of an autoinjector technology. The auto injector device consists of a spring loaded needle that works at the tip of the device to deliver the medication via intramuscular injection. The device has labeled end caps - a safety cap at one end, a needle cap for a built in needle protection at the other end, an easy grip body placed inside a carton with appropriately colour coded and numbered instructions. There are only two doses of adrenaline auto-injector commonly available: 0.15 mg and 0.3 mg. The more appropriate dose for an auto-injector should be prescribed for individual patients by allergy specialists.

It is available as either 0.15 mg or 0.3 mg unit disposable system i.e 0.15 mL or 0.3 mL of adrenaline for administration in patients weighing between 15-30 kg and those weighing more than 30 kg respectively at 1:1000 dilution for a single use. They usually contain more than the required dose of the drug which will be left over in the syringe after a single fixed dose administration. This spare volume of the drug cannot be further utilised and should be discarded along with the device.

Route of administration:

Adrenaline autoinjector is meant only for injection into the anterolateral aspect of thigh through intramuscular route. Even though adrenaline can be administered through various routes the preferred route of administration in anaphylactic shock is through intramuscular route. It has been observed that adrenaline given by intramuscular route has a faster onset of action than the subcutaneous route. A needle of adequate length enough to ensure that the medication is injected into the muscle should be used. The intramuscular adrenaline dose can be repeated at 5-minute intervals if there is no improvement in the patient’s condition.

The subcutaneous route of administration is not very effective due to poor vascularity of the subcutaneous tissues which will be further compromised during a vascular shock. This delay in absorption may have important clinical implications during an episode of systemic anaphylaxis and hence intramuscular route of injection is preferred.

How to use adrenaline autoinjector:

The adrenaline auto injector device should be used with caution. The prescribing physician has to appropriately instruct the patient or the caregiver regarding methods of administration of the injection and proper handling of the device.

The drug in the device has to be inspected for any colour change, presence of impurities, expiration date before administration. It should be protected from light and stored at a temperature of 20-25 degree C. Adrenaline can deteriorate rapidly on exposure to air or light. A fist is formed around the autoinjector with the needle tip pointing downwards. The safety cap should be removed only at the time of administration. Press and hold technique is used while administration. i.e pressing hard and holding
the device in the middle of the outer side of thigh for 10 seconds. This will release the spring loaded needle that is designed to deliver the full dose of the medication. The device should then be carefully removed from the injection site and reinserted into the carrying carton. Immediate medical attention should be sought after use. The used device should be taken along with the patient for expert opinion and further guidance. The remaining amount left over should never be reused.

New advances

The U.S. FDA has approved a new auto injector during August 13, 2012. It is a rectangular device 3.5 inches by 2 inches by 0.5 inch. It has a sound chip in it to provide audio cues to the patient or the caregiver to assist with the proper use of the device. During a life-threatening allergic reaction the new device talks the user through each step of the injection process. If the patient or caregiver needs more time, it repeats the step-by-step directions. Alternatively, a patient or caregiver can also use the written instructions printed on the device for administration guidelines. It provides users with audible and visual cues, including a five-second injection countdown and an alert light to signal when the injection is complete. In addition to being an auto-injector, it features an automatic retractable needle mechanism to help prevent accidental needle sticks. Available in two different dosages, the new device delivers 0.3 mg adrenaline injection. It can be used for patients who weigh 66 pounds or more. Another delivers 0.15 mg adrenaline injection and it can be used for patients who weigh 33 to 66 pounds. The new version has not been studied in patients weighing less than 33 pounds. Each pack contains two devices containing one dose of adrenaline for therapeutic use and another non-active training device.

In 2013 another auto injector fitted with 25 mm needles to the 300 mcg and 500 mcg models has been approved by the UK MHRA.

Limitations of auto injector devices:

Failure to demonstrate the correct use of the device by health care professionals, incorrect self-administration technique, incorrect route of administration, suboptimal injection, needle-stick injury, poor absorption and adrenaline resistance, outdated auto-injectors, large size of devices, lack of standardized assessment criteria are the limitations that have been encountered with the use of adrenaline auto injector devices. In addition, further problems of activation force, spring force and delivery location of the medication, as well as the robustness of the device should be taken into consideration.

It has been noted that the effective needle length or depth of delivery was 21 mm which is better than the conventional syringe. The adrenaline autoinjector delivers the drug with a needle length of 1.4 cm. The distance from skin to muscle in the anterolateral aspect of the thigh shows that this length is less for the proper delivery of the drug 18.

An international survey conducted by the world allergy organization has shown that adrenaline auto-injectors were available in about half of surveyed countries and that the cost of an auto-injector in some countries was equivalent to the monthly salary of an average citizen. Of 39 countries, auto-injectors containing 0.15 mg and 0.3 mg doses were available in 17 (44%) and 22 (56%), respectively.

Related to the problems encountered with the use of current adrenaline auto-injectors, an ‘ideal’ device should be able to deliver adrenaline to the correct tissue compartment, it must deliver adrenaline within the correct time frame, it must deliver the correct dose of adrenaline, it must be robust and reliable enough to withstand real-life use, it must be easy, convenient and safe for patients or caregivers to use.

Cautions and Adverse Effects of adrenaline autoinjector:

The autoinjector should never be injected into the buttock or intravenously. If accidentally injected into any other part of the body, immediate medical treatment should be sought. The most common side effects may include increase in heart rate, sweating, nausea and vomiting, difficulty breathing, paleness, dizziness, weakness or shakiness, headache, apprehension, nervousness, or anxiety.

Careful history on concomitant medications and comorbid conditions should be elicited before prescribing an auto injector device of adrenaline. The prescriber should carefully assess the exact need for the auto injector device and the particular dose needed, according to the weight of the patient as only two dose strengths are available for use. It is not advisable to administer more than two sequential doses except under medical supervision.

Accidental parenteral injections of adrenaline by autoinjector do occur. In general the injection sites are digits, palm and rarely thigh. The symptoms include swelling, pallor, pain, and erythema.

Local injection of phentolamine is effective for up to 13 hours after the inadvertent digital instillation of adrenaline.
Restricted use and need for global awareness: Adrenaline auto-injectors are underused by patients for a variety of reasons. In some countries, they are not available. In others, they are not affordable or not prescribed when indicated, for example, at the time of discharge from an emergency department after treatment for an acute anaphylaxis episode, or because previous reactions were considered to be mild. The World Allergy Organization ad hoc Committee has pointed out the fact that adrenaline is currently being underutilized, often dosed suboptimally to treat anaphylaxis, is being under prescribed for potential self-administration and that the therapeutic benefits of adrenaline outweigh the risk associated with its intramuscular use. In spite of the fact that adrenaline is an established therapy for treatment of acute anaphylaxis the use of adrenaline is still much restricted which is in part related to a reluctance to prescribe them. This has been highlighted in a report conducted by the Anaphylaxis Campaign.

Several studies have shown that auto injectors are being prescribed for adult patients with food allergy. In addition autoinjectors are also used in children with food and related allergies as a part of medical emergency response plans. But it has been observed that there is an overall under prescription of epinephrine autoinjectors in school going adolescents. It has been shown through an analysis of data from a national case registry of fatal food anaphylaxis in the U.S. that only very few individuals had adrenaline autoinjectors available at the time of fatal reaction. Adrenaline injected by an auto-injector into the anterolateral aspect of the thigh is the gold standard of care in the management of acute anaphylaxis. There is a strong and urgent need for a coordinating expert panel of concerned health care professionals for framing a geographical variation oriented anaphylactic treatment plan for appropriate use of adrenaline and an appropriate device modification strategy to suit the population along with patient educational guidelines. This to a great extent can improve patient outcome measures in acute anaphylaxis.

Adrenaline auto-injector is only an emergency supportive care therapy that can be used in circumstances by the patient or a first responder where medical facilities are not at hand. It is a supportive therapy and cannot be a substitute for immediate medical attention.

Patient Education: All patients should be adequately informed and well educated regarding the seriousness of an anaphylactic episode and the need to be cautious. They should be educated on the causative allergen responsible for their anaphylactic reaction and how to avoid exposure to it in future. In addition an awareness on the mode of onset of the early symptoms of anaphylaxis along with the instructions of how to use their adrenaline auto-injector, and the importance of seeking urgent medical assistance when experiencing anaphylaxis symptoms or after using an adrenaline auto-injector must be briefed in detail.

Anaphylaxis education about how, when and why to use an adrenaline auto-injector, remains critically important. Healthcare professionals need to be trained to use adrenaline auto-injectors in order to train the patients at risk of anaphylaxis as well as their caregivers as how to use them correctly and safely. There is a clear need to improve the education of both the patients and the physicians on the use and indications of adrenaline auto-injectors.

Conclusions

Anaphylaxis is an acute and potentially life threatening immediate hypersensitivity reaction. Consensus opinion and anecdotal evidence recommend adrenaline administration as early as possible as soon as the initial symptoms occur, because fatalities in anaphylaxis are the result of delayed or inadequate administration of adrenaline. Thus adrenaline injected by an auto-injector into the anterolateral aspect of the thigh without delay is the gold standard of care in the management of acute anaphylaxis. There is a strong and urgent need for a coordinating expert panel of concerned health care professionals for framing a geographical variation oriented anaphylactic treatment plan for appropriate use of adrenaline and an appropriate device modification strategy to suit the population along with patient educational guidelines. This to a great extent can improve patient outcome measures in acute anaphylaxis.

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