Anaphylactic Reaction : An Overview

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Introduction

Anaphylaxis is a life-threatening type I hypersensitivity reaction, triggered by exposure to a wide range of antigens and involving multiple organ systems. Anaphylaxis is not common, but prevalence and incidence figures in general population are unavailable because it is not a reportable disease. The diagnosis must be made on the basis of clinical findings and treatment initiated with the greatest urgency because the mortality rate approaches 10% in anaphylactic shock. Allergic reactions under anaesthesia occur once in every 5,000-25,000 anaesthetics with a 3.4% mortality which is significantly lower than that in general medical practice [1]. Reactions to insect stings alone are responsible for at least 50 deaths in the United States each year. All physicians, specialists and medical officers alike, need to be aware of the suddenness with which symptoms, severe reactions, and even death can occur in otherwise healthy persons. Rapid institution of appropriate treatment is essential for a favourable outcome. Anaphylactic reaction is briefly discussed in the present paper and the approach to the management of such reaction is outlined.

Mechanisms and Causes

The interaction of allergen and immunoglobulin E (IgE) antibody triggers mediator release, resulting in the reaction affecting multiple target organs. The release of mediators such as histamine and many others, from the mast cells and basophils is responsible for the immediate clinical manifestations of anaphylaxis. A late-phase response caused by the recruitment of other inflammatory cells, including eosinophils, can occur hours after the initial reaction. Anaphylaxis is usually thought of as an IgE-mediated allergic reaction to such things as foods, insect venoms, drugs, and latex. The mast cell, however, can be induced to react by other non-immunologic means, including [1] direct activation by exercise, opiates, and possibly radiocontrast agents, [2] disturbances of arachidonic acid metabolism by cyclo-oxygenase inhibitors such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), and [3]

complement activation by immune complexes, caused by reactions to blood products and resulting in production of complement C3a and C5a [2]. This is the mechanism for anaphylactoid reactions where the term 'anaphylactoid' is used to designate reactions that are indistinguishable from anaphylaxis but lack a demonstrable IgE allergic mechanism. Some anaphylactoid reactions are triggered by an identifiable agent, such as a drug that possesses the pharmacologic property of causing direct, nonimmunologic release of mast cell mediators. Certain intravenous anaesthetic agents, muscle relaxants, protamine, aspirin and nonsteroidal antiinflammatory drugs, opiates, and iodinated contrast media used in radiography are the most common agents with this property. In other cases, the reaction is triggered by a physical activity such as exercise, and a few patients have recurrent idiopathic "anaphylaxis".

Some patients have repeated anaphylactic episodes without the cause being determined. In a recent study of 266 patients referred for evaluation when obvious causes (eg, insect stings, immunotherapy) had been eliminated, 37% were determined to have idiopathic disease [3]. In patients in whom a cause was identified, common triggers included foods (eg, peanuts, fish, nuts, eggs), drugs (NSAIDs, aspirin, penicillin, cephalosporins, insulin, sulfonamides, blood products, vaccines, and enzymes such as trypsin, chymopapain, and streptokinase), exercise, and latex.

Clinical features

Anaphylactic shock is caused by vasodilation and vascular leakage resulting from enhanced permeability of the postcapillary venules in the vascular beds of visceral organs, skin, and mucous membranes. Bronchial and gastrointestinal muscle spasms produce acute airway obstruction and colicky abdominal pain. Increased vascular permeability in the skin results in pruritus, urticaria, and angioedema.

The clinical manifestations of anaphylaxis can occur within seconds of antigen exposure. With fatal reactions, the respiratory and cardiovascular systems are often

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affected initially. Respiratory manifestations include stridor, difficulty in breathing, cyanosis and even pulmonary oedema. Severe upper airway obstruction by angioedema can lead to asphyxia while lower airway obstruction with wheezing and chest tightness is caused by bronchospasm. Laryngeal oedema may be experienced as lump in throat. The commonest cardiovascular manifestation is severe hypotension, usually caused by a massive shift of fluid from the intravascular to the extravascular space. Arrhythmias are not uncommon. Profound losses of intravascular volume can occur quickly as a result of increased vascular permeability. Patients compensate through maximal vasoconstriction initiated by the release of catecholamines and angiotensin.

Gastrointestinal symptoms include nausea, vomiting, diarrhoea, and abdominal pain. Flushing, diaphoresis, urticaria, pruritus and angioedema are cutaneous signs. Patients may experience a feeling of impending doom and light headedness and sometimes sense a metallic taste in the mouth. In most cases, the slower the onset of symptoms, the less severe is the reaction. Some patients experience recurrence of symptoms hours after apparent remission of the initial reaction (late-phase anaphylaxis). In patients taking beta-blockers, anaphylaxis is often severe and may be refractory to conventional management [4].

Differential diagnosis

When a patient presents with sudden symptoms of dizziness, syncope, or flushing, rapid assessment is essential so that an appropriate course of management can be determined. Many conditions need to be considered (Table-1). The vasovagal reaction is the one most commonly confused with anaphylaxis [5]. It usually follows a painful intervention such as an injection and is manifested by pallor, light-headedness, nausea, profuse diaphoresis and syncope. Symptoms improve promptly with recumbency and disappear altogether without treatment in 20 to 30 minutes. The lack of pruritus in the presence of a slow pulse rate and normal blood pressure distinguishes a vasovagal attack from anaphylaxis.

Ingestion of spoiled fish from the tuna family may result in urticaria, pruritus, flushing, gastrointestinal upset, and headache. The cause of this reaction is, a histamine like substance (saurine) produced through bacterial contamination. Other factors, such as the presence of a carcinoid tumour or a reaction between alcohol and chlorpropamide, can cause flushing-type reactions. Psychosomatic conditions can present as vocal cord dysfunction or outright fictitious anaphylaxis.

Table 1

Differential diagnosis of suspected anaphylaxis

Cardiac arrhythmia
Myocardial infarction
Bronchial asthma
Aspiration of gastric contents
Seizure disorder
Insulin reaction
Pulmonary embolism
Pneumothorax
Flushing syndromes
Globus hystericus
Vaso-vagal reactions
Fictitious allergic reactions

Treatment

Treatment of anaphylaxis consists of both short and long term management (Table-2). The immediate goal is to maintain an adequate airway and support the blood pressure. Patients having severe reactions should be given oxygen. Epinephrine should be administered as soon as the diagnosis is made. Conventionally it is given subcutaneously every 10 to 20 minutes until the patient's condition is stable. However, in life-threatening reactions with shock, intravenous administration may be necessary, this route, however, poses risks of ventricular arrhythmias and myocardial ischemia. For this reason, intravenous epinephrine is given slowly in low doses. Commonly available ampoule of adrenaline when diluted in a 10 ml syringe will have a concentration equivalent to 1:10000 solution. It should be given over at least a 10 minute period, but the dose is usually limited to 3 mL for an average sized (70 kg) adult [6]. Continuous infusion may subsequently be needed to sustain the blood pressure [7]. Hypotension should be treated with intravenous fluids to expand the intravascular volume. Colloids, when available, may have an advantage over crystalloid solutions because colloids remain in the intravascular space and potentially attract extravasated fluid into the vascular space [6].

Antihistamines are useful as second line therapy when a prolonged course is suspected. Diphenhydramine hydrochloride can be given orally, intramuscularly, or intravenously. The combined use of H₁ and H₂ histamine antagonists is controversial, but cimetidine has been used. Corticosteroids may not be helpful in immediate management of anaphylaxis but can be useful in treating prolonged urticaria or a late phase response. Methylprednisolone sodium succinate is usually given in large doses every 6 hours. Bronchospasm should be treated with inhaled beta2 agonists, with the option of using intravenous aminophylline in resistant cases.

Refractory anaphylaxis in patients receiving beta-

Table 2

Management of anaphylaxis

Stop further administration of any possible suspected antigen

First line therapy	Second-line therapy	Third-line therapy
Airway maintenance, think of tracheal intubation as larynx can become oedematous	Diphenhydramine HCl, 50 mg PO, IM, or IV	Histamine2 antagonists Cimetidine 4-8 mg/kg, Ranitidine 1 mg/kg 6 hourly
100% Oxygen	Methylprednisolone sodium succinate, 125 mg IV or Hydrocortisone 2-4 mg/Kg 3-6 hourly or Dexamethasone 0.1-0.2 mg/kg 4-6 hourly	Glucagon.* 1 mg ampoule 40 mcg/kg bolus (1-2 mg) stat followed by 10-50 mcg/kg/hour IV infusion
Epinephrine SC: 0.01 mL/kg, to maximum of 0.3 to 0.5 mL, of 1:1000 aqueous solution (1 mg/mL)	Bronchodilators: Inhaled beta2 agonists, Salbutamol 100 mcg/puff 1-2 puffs 4-6 hourly	Atropine sulfate,* 1 mg IV
IV: 1 to 3 mL of 1:10,000 aqueous solution (0.1 mg/mL) given over 10 min, or 1 to 4 micrograms/min (0.25 to 1 mL/min of a solution of 4 microgram/ml made with 1 ml of 1:1,000 epinephrine in 250 mL fluid)	Nebulize Salbutamol 50-150 mcg/kg per dose every 20 min IV aminophylline 5 mg/kg bolus slowly, 0.9 mg/Kg/hour infusion Terbutaline SC 0.01 mg/kg Q 15 min, 3 doses	
Fluids 10 to 20 mL/kg of 6% hetastarch in normal saline or 5% human albumin solution or haemaccel or 5% dextrose in 0.5N saline solution or lactated Ringer's solution	Vasopressors: Norepinephrine 0.05-0.1 mcg/kg/min or Dopamine 5-10 mcg/kg/min	Isoproterenol,* 0.1 micrograms/kg per minute initially, with increases at this rate every 10 minutes until blood pressure is stabilized or heart rate reaches 200 beats per minute (use only in healthy children and young adults without heart disease) (mix 2.5 mL of 1:5,000 isoproterenol solution [0.2 mg/mL] in 50 mL fluid to equal 10 micrograms/mL)

*Useful in refractory anaphylaxis induced by beta-blocker therapy

blocker therapy requires the use of additional agents [4]. Some success has been achieved with glucagon, which may increase cardiac cyclic AMP, thereby enhancing cardiac output. This agent is available as a 1 mg ampoule than can be given intravenously as often as every 5 minutes because of its short half-life. Intravenous atropine is also recommended for refractory bronchospasm. Beta blockers act as a competitive inhibitor of catecholamines, and beta 2 agonists given in high doses may counteract this effect. Isoproterenol hydrochloride is one such agent, however, it should be avoided when possible in adults, particularly those with heart disease, because myocardial ischemia can result [8].

Once the acute event is under control, further management should be directed towards confirming the diagnosis of anaphylaxis, identification of the suspected allergen and proper documentation. Laboratory diagnosis of anaphylaxis is retrospective because of rapidity of onset. However, several uncommon tests may

substantiate the diagnosis. Sequential blood samples should be taken in a glass tube as soon as possible and then 1 and 6 hours after the reaction for further analysis. Plasma histamine level is elevated but has a very short half life making detection difficult even during the event. Serum IgE and complement levels fall whereas activated forms of complement show an upward trend. Recently, estimation of mast cell tryptase levels have been described which rise an hour after the episode and remain elevated for four hours and thus aid the investigation of anaphylactic reaction much after the event. Tryptase is a mast cell derived natural protease with a half life of 60-90 minutes.

The entire clinical records should be completed and the patient should be explained the implications of the event. He should subsequently be referred to an immunology and allergy laboratory for further investigations such as skin tests and other specialized tests. Meanwhile he should be advised to wear a medic-alert bracelet.

Prevention

The most important component of anaphylaxis management is prevention (Table-3). Identification and subsequent avoidance of the offending allergen or other nonimmunologic causes seems an obvious first step. If there is definite history of past anaphylactic reaction, it is advisable to select another agent / procedure. Since stinging insects cannot be consistently avoided, venom immunotherapy, when possible, offers an effective means of preventing life-threatening reactions. Patients, who are sensitive to radiocontrast material, have a history of venom-sensitivity or are receiving immunotherapy injections, should be advised to discontinue beta blocker therapy beforehand. An effective pre-treatment schedule consisting of corticosteroids, antihistamines, and ephedrine sulfate has been described for patients with a history of reactions to radiocontrast materials who are undergoing repeated studies [9]. Long term oral corticosteroid therapy every other morning has been advocated for patients with life-threatening idiopathic anaphylaxis [10].

Table 3

Measures to prevent anaphylaxis

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- * Following an event, maintain a high index of suspicion.
 - * Identify and avoid allergens or other causes.
 - * Encourage high-risk patients to wear medical identification containing relevant information.
 - * Provide immunotherapy for venom-sensitive patients.
 - * When possible, use oral route for drugs.
 - * Observe patient for 30 minutes after initial dose of a high-risk drug. If possible administer a test dose followed by slow administration of full dose.
 - * Instruct patients to avoid exercise for 1 hour before and several hours after high-risk procedures.
 - * Discontinue beta-blocker therapy during periods of high risk.
 - * For patients with sensitivity to radiocontrast agents, provide pretreatment as follows: 1) 50 mg of prednisone given 13, 7 and 1 hour before procedure using radiocontrast material, 2) 50 mg of diphenhydramine HCl given 1 hour before procedure, 3) 25 mg of ephedrine sulfate given 1 hour before procedure. This regime may be used for other drugs in a modified manner i.e. dexamethasone or methylprednisolone in fewer doses.
 - * Prescribe epinephrine for high-risk patients and instruct them in self-administration.
 - * If a specific drug must be administered to a patient with known allergy, a course of pre-treatment should be given as above, an intravenous infusion should be started and all facilities for resuscitation and intubation should be kept readily available.
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All patients at risk for anaphylactic reactions should be given a prescription for an emergency epinephrine kit or syringe and instructions on self-administration. Patients need to make arrangements to have the kit readily available in the event of a reaction, since a short delay in administration can be fatal. The kit or syringe should

be readily available at all times. Exposure to air and light can cause the epinephrine to oxidize and turn brown, at which point the syringe should be replaced. An emergency self-administration kit usually contains a syringe, tourniquet, chlorpheniramine maleate tablets, and an alcohol swab. The syringe has a 25 gauge needle and is operated manually, so there is little chance of accidental injection. A maximum dose of 0.3 mL of 1:1,000 epinephrine can be delivered at once, and graduations on the syringe barrel allow delivery of smaller doses for children. A second 0.3-mL dose can be delivered if symptoms do not improve.

Summary and Conclusion

Anaphylaxis is a potentially fatal condition. Causes range from bee stings to drugs, foods, and exercise. Onset is usually sudden, and a delayed reaction may occur hours after the initial reaction. Treatment consists of airway maintenance and support of the blood pressure with fluid expanders, epinephrine and oxygen. Additional agents, such as corticosteroids, antihistamines, vasopressors, glucagon, atropine sulfate, and isoproterenol hydrochloride, can be useful. Prevention is the most important part of anaphylaxis management. In patients with known allergies, self-administration of epinephrine plays a key role in reducing mortality.

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