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REVIEW ARTICLE

Anaphylactic shock: mechanisms and treatment

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SUMMARY

This paper reviews the mechanisms of anaphylactic shock in terms of the immunoglobulin and non-immunoglobulin triggering events, and the cellular events based on the rise in intracellular cyclic AMP and calcium that release preformed granule-associated mediators and the rapidly formed, newly synthesized mediators predominantly based on arachidonic acid metabolism. These primary mediators recruit other cells with the release of secondary mediators that either potentiate or ultimately curtail the anaphylactic reaction. The roles of these mediators in the various causes of cardiovascular collapse are examined. The treatment of anaphylactic shock involves oxygen, adrenaline and fluids. The importance and safety of intravenous adrenaline are discussed. Combined H_1 and H_2 blocking antihistamines and steroids have a limited role. Glucagon and other adrenergic drugs are occasionally used, and several new experimental drugs are being developed.

Key words: adrenaline, anaphylactic shock, anaphylaxis, histamine H_1 receptor blockaders, histamine H_2 receptor blockaders

INTRODUCTION

The first case of anaphylaxis was recorded on the tomb of King Menes, an Egyptian Pharaoh who died suddenly in 2640 BC following a wasp sting.[1] The term anaphylaxis is derived from the Greek and means literally 'against protection'.[2] It was introduced in 1902 by Charles Richet and Paul Portier following experiments with unexpected fatal reactions on dogs sensitized to Portuguese man-of-war venom, observed the previous year whilst on board Prince Albert of Monaco's yacht in the Mediterranean. Richet was subsequently awarded the Nobel Prize in Medicine and Physiology in 1913.[3]

At around the same time, in 1906, Von Pirquet introduced the term 'allergy' although he assumed that the major allergic diseases, such as urticaria and asthma, were due to the absence of antibodies.[4] In 1921, Prausnitz and Küstner demonstrated the ability to transfer a serum factor (termed *reagin*) in the serum of a sensitive patient to a non-sensitive recipient, although it was not until 1967 that Ishizaka and colleagues identified this reagin as a new class of immunoglobulin known as IgE. Finally, in 1975, Coombs and Gell classified hypersensitivity reactions into three immediate types and one delayed type, although in practice these types need not necessarily occur in isolation from each other.[5] In immunological terms, anaphylaxis is an example of an immediate, Type-1 hypersensitivity reaction.

DEFINITION

Currently, the term anaphylaxis is best used to describe the rapid, generalized and often unanticipated, immunologically mediated events that occur after exposure to certain foreign substances in previously sensitized persons. Anaphylactoid reactions describe a clinically identical syndrome involving similar mediators but not triggered by IgE antibody and not necessarily requiring previous exposure. Despite important aetiological distinctions, the term anaphylaxis is commonly used to describe both of these clinical syndromes, even when the mechanisms are unknown.[3] The most common life-threatening feature of acute anaphylaxis is cardiovascular collapse or shock. Other life-threatening effects include bronchospasm, angio-oedema and pulmonary oedema.[6,7] This paper will focus on the mechanisms and both general and specific treatment of anaphylactic shock.

MECHANISMS OF ANAPHYLACTIC SHOCK

Mechanisms of anaphylactic shock may be divided

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into four main categories: the events that trigger the anaphylactic reaction; the cellular events that then lead to mediator release; the clinical pharmacology of these mediators; and finally the cardiovascular responses of patients to these mediators.

MECHANISMS: TRIGGERING EVENTS

The events that trigger anaphylaxis are either anaphylactic and IgE immunologically mediated, or anaphylactoid and non-immunoglobulin mediated, although in many reactions there is evidence of the involvement of multiple pathways (see Table 1).

ANAPHYLACTIC IgE ANTIBODY REACTIONS

Most cases of anaphylaxis are IgE, or rarely IgG_4, mediated.[8] Following previous exposure to an antigen, IgE reaginic antibodies are released into the circulation by plasma cells derived from B-lymphocytes, under the influence of helper T-cells. These antibodies bind to glycoprotein receptors on tissue mast cells or blood-borne basophils, thereby sensitizing them. Subsequent re-exposure to the antigen cross-links the Fab portions of two surface-bound IgE molecules, activating the cell and triggering the release of chemical mediators.[9,10] In normal subjects there are up to 100 000 surface-bound IgE molecules per mast cell, and in atopic subjects up to half a million.[11]

A vast range of substances induce IgE antibody formation (see Table 2), including the following: protein drugs such as insulin and ACTH; non-protein drugs acting as haptens such as antibiotics, vitamins and steroids; vaccines; foods, including milk, fish and nuts; venoms, particularly of Hymenoptera; and many other substances as diverse as ethylene oxide, hydatid cysts and latex.[8] Latex allergy was first reported in 1979, and has caused intra-operative anaphylactic reactions.[12] In addition, allergy to the latex catheter-tip used in barium enemas has also been recorded, most commonly in children with spina bifida or congenital urological abnormalities.[13]

Table 1. Causes of anaphylaxis/anaphylactoid reactions

Anaphylactic: IgE mediated
See Table 2
Anaphylactoid: Non-IgE mediated
(1) Complement activation
(a) Classical pathway
(b) Alternate pathway
(2) Coagulation/fibrinolysis system activation
(3) Direct pharmacological release of mediators
(a) Direct histamine release
(b) Modulators of arachidonic acid metabolism
(c) Sulphiting agents
(4) Physical
(a) Exercise induced
(5) Idiopathic

ANAPHYLACTOID REACTIONS

Anaphylactoid reactions are non-immunoglobulin mediated and are caused by mediator release that is triggered independently of reaginic antibodies. These reactions do not require prior exposure, and patients may not react on every occasion. Anaphylactoid reactions may be due to complement activation, coagulation/fibrinolysis system activation, or the direct pharmacological release of mediators.[8]

COMPLEMENT ACTIVATION

Complement activation via the classical pathway or alternate pathway leads to the formation of anaphylatoxins C3a, C4a and C5a. These anaphylatoxins stimulate mast cells and basophils to degranulate, releasing mediators that cause local and systemic reactions. C3a and C5a also directly induce increased vascular permeability, smooth muscle contraction and neutrophil chemotaxis.[14,15]

COAGULATION/FIBRINOLYSIS SYSTEM ACTIVATION

Activation of the coagulation/fibrinolysis system via Hageman Factor XII leads either to plasmin production and activation of complement, or to the production of kinins such as bradykinin that cause vasodilatation and increased vascular permeability.[8,11]

DIRECT PHARMACOLOGICAL RELEASE OF MEDIATORS

The pharmacological release of mediators is seen with opioids or radiocontrast media that release histamine directly.[16,17] Alternatively, aspirin and other non-steroidal anti-inflammatory drugs modulate arachidonic acid metabolism by

Table 2. Common causes of IgE antibody formation

(1) Protein drugs (hormones)
Insulin, ACTH, vasopressin
(2) Non-protein drugs (haptens)
(a) Antibiotics
Penicillin, sulphonamides, cephalosporins
(b) Vitamins
Thiamine, folic acid
(3) Vaccines (allergy probably to cultivating tissue)
Pertussis, typhoid
(4) Foods
Eggs, fish, nuts, chocolate, fruits
(5) Venoms
Bee, wasp, fire ant, snake
(6) Foreign protein agents
Tetanus antitoxin, gamma globulin, venom antitoxin, semen
(7) Enzymes
Trypsin, chymotrypsin, penicillinase
(8) Allergen extracts
Pollen, mould, animal dander
(9) Chemicals
Ethylene oxide gas, formaldehyde
(10) Parasites
Hydatid cyst rupture
(11) Latex
Surgical gloves, catheter-tip

interfering with the cyclo-oxygenase pathway, leading to enhanced formation of lipoxygenase products such as the leukotrienes. Mast cell degranulation is not involved.[14]

RARE, PHYSICAL AND IDIOPATHIC CAUSES

Rare causes of anaphylactoid reactions include sulphiting agents used as food preservatives, and exercise-induced anaphylaxis, first described in 1980, in which anaphylaxis is triggered by exertion, or exertion following food or specific single food items.[18,19] Finally, idiopathic anaphylaxis is most commonly seen in adults, the majority of whom are asthmatic or atopic and who, after exhaustive testing, are found to have no known cause of anaphylaxis.[20,21]

MECHANISMS: CELLULAR EVENTS

Regardless of which of the above mechanisms triggers anaphylaxis, the cellular events leading to mediator release are similar. All the signs and symptoms of anaphylaxis may be produced by histamine. More severe reactions are usually correlated with higher histamine levels. However, fatal reactions have occurred without elevation of plasma histamine, suggesting that other equally important mediators are involved. Mast cells and circulating basophils are the key cells in the allergic response, and produce two main groups of mediators following triggering.[22]

PRIMARY, PREFORMED, GRANULE-ASSOCIATED MEDIATORS

First, antigen cross links two surface-bound IgE molecules causing a transmembrane coupling protein to activate adenyl cyclase. This leads to a short-lived rise in intracellular cyclic AMP, activating protein kinases that catalyse the phosphorylation of certain cell proteins. A complex series of reactions, with microtubule formation allowing the movement of preformed granules towards the cell membrane, results in the release of granule-associated mediators into the intercellular space.[10,23] Primary, preformed, granule-associated mediators include the vasoactive mediator histamine, chemotactic mediators such as neutrophil chemotactic factor and eosinophil chemotactic factor, enzymes such as tryptase, chymase and beta-glucuronidase, and proteoglycans such as heparin and chondroitin sulphate[24] (see Table 3).

Table 3. Preformed mast cell mediators

(1) Vasoactive mediator
  Histamine

(2) Chemotactic mediators
  (i) Neutrophil chemotactic factor
  (ii) Eosinophil chemotactic factor

(3) Enzymes
  (i) Neutral proteases
    (a) Tryptase
    (b) Chymase
  (ii) Acid hydrolases
    (a) Beta-glucuronidase
    (b) Beta-hexosaminidases
    (c) Arylsulphatase A

(4) Proteoglycans
  (i) Heparin
  (ii) Chondroitin sulphate

RAPIDLY FORMED, NEWLY SYNTHESIZED MEDIATORS

Secondly, antigen causes receptor perturbation with the simultaneous opening of surface membrane calcium channels allowing an influx of calcium ions into the mast cell, leading to activation of phospholipase A_2.[10,11] This enzyme breaks down membrane phospholipids to release arachidonic acid and lysophospholipid. Arachidonic acid is then oxygenated by the cyclo-oxygenase pathway to form prostaglandins and thromboxanes, or by the lipoxygenase pathway to form leukotrienes. These rapidly formed, newly synthesized primary mediators include the following: prostaglandin D_2; thromboxane A_2; leukotrienes such as B_4 (LTB_4) and C, D and E_4 (LTC_4, LTD_4 and LTE_4) previously called slow-reacting substance of anaphylaxis; platelet-activating factor (PAF); cytokines such as tumour necrosis factor and interleukins; adenosine and free oxygen radicals[15,24] (see Table 4).

At a cellular level, mediator release may be modulated by the steady-state, resting intracellular cyclic AMP levels. The importance of this is that substances that elevate cyclic AMP, such as adrenaline, inhibit mediator release, whereas substances that decrease cyclic AMP or increase reciprocal changes in cyclic GMP, such as cholinergic agents, augment mediator release.[5,11]

MECHANISMS: CLINICAL PHARMACOLOGY

For simplicity, the actions of these primary mast cell and basophil mediators may be divided into three categories[5] (see Table 5). First, histamine, PAF, tryptase and bradykinin are inflammatory activators that induce vasodilatation and oedema. Secondly, histamine, prostaglandin D_2, LTC_4 and LTD_4 are spasmogens that cause bronchial smooth muscle contraction, increased mucus production and mucosal oedema. Prostaglandin D_2 is ten times more potent as a bronchoconstrictor than

Table 4. Rapidly formed, newly synthesized mast cell mediators

(1) Arachidonic acid metabolites
  (i) Cyclo-oxygenase pathway
    (a) Prostaglandin D_2
    (b) Thromboxane A_2

  (ii) Lipoxygenase pathway
    (a) Leukotriene LTB_4
    (b) Leukotrienes LTC_4, LTD_4, LTE_4
      (formerly called SRS-A: slow reacting substance of anaphylaxis)

(2) Platelet-activating factor (PAF)

(3) Cytokines
  (i) Interleukins
  (ii) Tumour necrosis factors (TNF)
  (iii) Granulocyte-macrophage colony-stimulating factor (GM-CSF)

(4) Adenosine

(5) Free oxygen radicals

Table 5. Actions of primary mast cell mediators

(1) Inflammatory activators
(a) Histamine
(b) PAF
(c) Tryptase
(d) Bradykinin
(2) Spasmogens
(a) Histamine
(b) Prostaglandin D_2
(c) LTC_4
(d) LTD_4
(3) Chemotactic agents
(a) Neutrophil chemotactic factor
(b) Eosinophil chemotactic factor
(c) LTB_4

histamine, and leukotriene D_4 is up to 1 000 times more potent.[25] Thirdly, neutrophil chemotactic factor, eosinophil chemotactic factor and LTB_4 are chemotactic agents that attract a variety of new cells to the area.

Thus platelets, neutrophils, eosinophils, lymphocytes, monocytes, mast cells and basophils are recruited to the area. These newly recruited cells in turn release secondary mediators of anaphylaxis such as histamine-releasing factor, major basic protein and lysosomal enzymes causing more inflammation and tissue destruction.[8,26] A further wave of mast cell degranulation is induced, leading to a vicious cycle of ongoing inflammation associated with increased vascular permeability.[24]

However, some of the secondary mediators released, in particular by eosinophils, inhibit anaphylaxis. For instance, histaminase breaks down histamine, arylsulphatase B inactivates the leukotrienes, and phospholipase D destroys PAF.[11] Furthermore, histamine itself, via H_2 receptors, elevates intracellular cyclic AMP, thereby reducing mediator release.[27,28] Thus the anaphylactic process may be self-limiting in less severe reactions.

MECHANISMS: CARDIOVASCULAR RESPONSES

The final consideration in discussing mechanisms of anaphylactic shock is the cardiovascular response in humans to the primary and secondary mediators mentioned previously. Cardiovascular collapse is common in severe anaphylaxis.[1,22] Arrhythmias, hypovolaemia, decreased myocardial contractility and pulmonary hypertension are all contributing factors[29] (see Table 6). Arrhythmias may be due to direct mediator effects, hypoxia, hypotension, pre-existing heart disease, acidosis or exogenous drugs such as adrenaline.[30] Hypovolaemia results from a plasma volume loss of up to 50% within 10–15 min in severe reactions.[31] This plasma volume loss is due to vasodilatation with the peripheral pooling of blood in large capacity splanchnic venous beds,[32] increased vascular permeability with a shift of intravascular fluid to the extravascular space, and decreased venous return from raised intrathoracic pressures from bronchospasm and positive pressure ventilation.[1] Decreased myocardial contractility is due to hypoxia, myocardial ischaemia, acidosis, direct mediator effects and exogenous drugs such as beta-blockers or calcium-channel blockers.[33,34] Finally, pulmonary hypertension is due to mediator-derived vasoconstriction and to the plugging of microvascular beds by aggregates of platelets and neutrophils with secondary vasoactive mediator release.[35,36]

Table 6. Causes of cardiovascular collapse in anaphylaxis

(1) Arrhythmias
(i) Direct mediator effects
(ii) Hypoxia
(iii) Hypotension
(iv) Acidosis
(v) Pre-existing cardiac disease
(vi) Exogenous drugs
(2) Hypovolaemia
(i) Vasodilatation
(ii) Increased vascular permeability
(iii) Decreased venous return
(3) Decreased myocardial contractility
(i) Hypoxia
(ii) Myocardial ischaemia
(iii) Acidosis
(iv) Direct mediator effects
(v) Exogenous drugs
(4) Pulmonary hypertension
(i) Mediator-derived vasoconstriction
(ii) Microvascular plugging

PRIMARY MYOCARDIAL DEPRESSION

There is controversy over the existence in humans of primary myocardial depression in anaphylaxis.[37] Many authorities believe that significant primary

cardiac depression is seen only in patients with pre-existing cardiac disease.[30,32] Others report cases of myocardial failure in patients without cardiac disease, although these are extremely rare.[38] There are histamine receptors on the heart, and *in vitro* histamine, prostaglandin D_2, PAF and leukotrienes C_4 and D_4 cause coronary artery vasoconstriction and negative inotropic effects that could all account for a degree of primary myocardial depression.[39] The situation is complicated by the observation that histamine H_2 receptors protect the heart by mediating coronary vasodilatation and increased myocardial contractility. Therefore, the use of H_2 receptor blockers in anaphylactic shock should cause further clinical deterioration. Paradoxically, the opposite seems to be true, indicating that other pathways are operating.[40,41]

TREATMENT OF ANAPHYLACTIC SHOCK

The explosive nature, unpredictable onset and usually rapid response to treatment that characterize anaphylactic shock mean that few controlled therapeutic trials have been undertaken on humans.[1] Despite attempts to avoid or prevent reactions, the vast majority of serious anaphylactic reactions occur unexpectedly.[3] Anaphylaxis is characteristically a disease of fit patients and is rarely seen or described in critically ill or shocked subjects other than asthmatics.[1] Recommended treatment is therefore based mainly on clinical anecdotes, understanding of the pathophysiology and, to a certain extent, animal studies.[6]

The severity of the reaction is related to the speed of onset of symptoms. Parenteral administration of antigen is the route most often implicated in severe anaphylaxis, with the majority of reactions to intravenous drugs occurring within 3 min.[42] In addition, oral, topical and inhalational exposure to antigen have all been associated with fatalities. Over 50% of people who die from anaphylaxis succumb within the first hour.[43] In 75% of cases the principal causes of death are asphyxia from upper airway oedema and hypoxia from severe bronchospasm. In 25% of deaths there is circulatory failure with hypotension.[44]

INITIAL MANAGEMENT: OXYGENATION

The initial management of anaphylactic shock includes a rapid assessment of the extent and severity of the reaction, establishment of the possibility of anaphylaxis, and cessation of further absorption of the suspected agent. Maintenance of an adequate airway, oxygenation, cardiac output and tissue perfusion with monitoring of vital signs, ECG and pulse oximetry are essential. A careful watch is kept for the development of laryngeal oedema or bronchospasm associated with the circulatory failure. Intubation and ventilation may be needed, and occasionally a surgical airway is required in the presence of gross laryngeal swelling. The shocked patient should be placed in

Table 7. Treatment priorities in anaphylactic shock

First line
(1) Oxygen and airway maintenance
(2) Adrenaline 1 in 100 000, 0.75–1.5 μg kg^{-1} IV at 1 mL (10 μg) min^{-1}. Follow by infusion at 1–4 μg min^{-1}
(3) Colloid 10–20 ml kg^{-1}IV.
Second line
(1) Diphenhydramine 25mg IV and cimetidine 300mg IV slowly over 3–5 min, repeated at 6-h intervals.
(2) Hydrocortisone 200mg IV at 6-h intervals
(3) Glucagon 1mg IV repeated at 5-min intervals, then infusion at 5–15 μg min^{-1} (especially if on beta-blockers)
(4) Vasopressors: noradrenaline (2–10 μg min^{-1}), dopamine (5–20 μg kg^{-1} min^{-1}) or metaraminol (30–200 μg mL^{-1}) to maintain desired BPI
Anecdotal/experimental
(1) Naloxone
(2) MAST suit
(3) Thryotropin-releasing hormone

IV, intravenous. All doses are quoted for a 70-kg adult.

the Trendelenburg position and rapid intravenous access secured to support the circulation. The mainstay of treatment for anaphylactic shock is oxygen, adrenaline and fluids.[1,3,22] (see Table 7).

ROLE OF ADRENALINE

Adrenaline should be given to all patients with significant hypotension, airway swelling or bronchospasm.[6] The actions of adrenaline reverse all features of anaphylaxis. Alpha-adrenergic stimulation increases peripheral vascular resistance and coronary artery perfusion raising the blood pressure, reverses peripheral vasodilatation and decreases angioedema and urticaria.[45] Beta-one-adrenergic stimulation has positive inotropic and chronotropic effects on cardiac muscle, and beta-two-adrenergic stimulation leads to bronchodilatation. Beta-adrenergic receptors also increase the production of intracellular cyclic AMP, which inhibits further mast cell mediator release.[46,47]

ADRENALINE: DOSAGE AND ROUTE

Unfortunately, the correct dosage and route of administration of adrenaline have been a source of confusion and conflict in the medical literature. For instance, the British National Formulary recommends 0.5–1.0 mg or 0.5–1 mL of 1 in 1000 adrenaline, administered intramuscularly, as the standard initial adrenaline regime in anaphylaxis.[48] In the USA, 0.3–0.5 mg of 1 in 1000 adrenaline, administered subcutaneously, is recommended.[3,14,26] In Sweden, 0.5–0.8 mg administered subcutaneously, is recommended.[49] The clinical effectiveness of these dose variations is not well defined, nor is there convincing evidence for any difference in effect between the subcutaneous and intramuscular routes.[6] The use of intravenous adrenaline in anaphylaxis is confounded by an even wider variation in proposed doses ranging from 1 $\mu g\,min^{-1}$ to a 2-mg bolus.[50,51] Many authors conclude that the use of intravenous adrenaline is too dangerous and rarely if ever justified, as it causes cardiac arrhythmias, myocardial ischaemia and severe hypertension.[52,53] However, cases cited from the literature to substantiate these claims fail to discuss the speed of delivery and concentration of the intravenous adrenaline administered, or to raise the possibility that other causes, such as hypoxia, hypotension, acidosis and direct mediator effects may have been responsible for the cardiovascular complications.[54,55]

Fisher's leader in the *British Medical Journal* in 1992 discussed the issues concerning the relevance and safety of intravenous adrenaline in anaphylaxis.[6] He noted that no one route of administration is likely to be right in all cases, and that the timing of administration of the drug may be critical. He suggested that, as vasodilatation is the main pathological change early in anaphylaxis, this enables the subcutaneous or intramuscular absorption of adrenaline to be rapid and effective. Thus, when the disease is treated early and is progressing slowly, or venous access is difficult or the patient is unmonitored, intramuscular adrenaline has advantages in terms of safety and is usually effective. Later, when intravascular volume is depleted and shock occurs, or there is severe dyspnoea or airway compromise, the intravenous route is necessary to achieve optimal absorption. In addition, Fisher considered that, in most cases, the recommended published intramuscular or subcutaneous doses were too high.

He advised doses of 0.3–0.5 mg of 1 in 1000 adrenaline administered subcutaneously or intramuscularly, and he recommended that the standard intravenous dose should be up to 3 mL of 1 in 10 000 adrenaline administered slowly. Fisher concluded with the diplomatic assertion that 'in severe anaphylaxis adrenaline by any route is better than none'.[6]

The Association of Anaesthetists of Great Britain and Ireland published a monograph in 1990 that further supports the importance and safety of intravenous adrenaline in anaphylaxis.[56] They recommended using adrenaline under ECG monitoring in an initial dose of 50–100 μg, particularly for hypotension or bronchospasm, followed by an infusion if prolonged therapy is required.

ADRENALINE: INTRAVENOUS DILUTION

Finally, there is disagreement over the correct dilution for the administration of intravenous adrenaline. Whilst the 1 in 10 000 dilution is favoured by some, a further tenfold dilution to 1 in 100 000 is suggested by many authors in order to minimize adverse reactions.[29,44–46,57] Thus Barach and Nowak recommend using 1 mL of 1 in 10 000 adrenaline diluted to 10 mL, giving a final concentration of 10 $\mu g\,mL^{-1}$, administered under

ECG monitoring at the rate of 10 μg or 1 mL min^{-1} [45] This may be followed by an infusion from 1–4 μg min^{-1}, according to Advanced Cardiac Life Support (ACLS) guidelines, adding 1 mg (1mL) of 1 in 1000 adrenaline to 250 ml of 5% dextrose in water, giving a final concentration of 4 μg mL^{-1}.[58]

ROLE OF FLUIDS

Fluid therapy is recommended alongside adrenaline in anaphylactic shock to replace the plasma losses of up to 50% of the circulatory volume. A bolus of 10–20 mL kg^{-1} of colloid, given rapidly, most effectively restores the circulatory volume.[23,59] Some authorities prefer crystalloid for volume loading.[44,57,60] Others suggest the use of fluids alone, questioning the central role of adrenaline.[61,62] However, adrenaline and fluids should be given together, as there are compelling arguments against using fluid alone, such as the additional efficacy of adrenaline in bronchospasm, urticaria and angioedema, its ability to stabilize mast cells and reduce further mediator release, and the speed at which it may be administered, particularly when intravenous access is delayed.[1]

USE OF ANTIHISTAMINES

The roles of all other drugs used in the treatment of anaphylactic shock are subsidiary to those of oxygen, adrenaline and fluids. In particular, antihistamines and steroids should never be relied upon alone as first-line therapy.[1,22] There is conflicting and inconclusive data with regard to the use of antihistamines in anaphylaxis. On the basis of an extensive review of current data, Lieberman concluded that for the prevention of drug-induced anaphylactic and anaphylactoid reactions, combined H_1 and H_2 receptor blockade is more effective than H_1 blockade alone.[63] Physiological rationale[64] and a series of case reports indicate that combined H_1 and H_2 receptor blockade should also be more effective than H_1 blockade alone in the treatment of anaphylaxis.[65,66] However, controlled clinical trials are still awaited to confirm this. Most importantly, antihistamines cannot have a central role in the management of anaphylaxis, as the concentration of histamine in the vicinity of a mast cell after degranulation is so great that, by the time anaphylaxis is diagnosed, it is too late for a competitive blocker to be of value. Furthermore, antihistamines do not actually prevent mediator release, and mediators other than histamine are of equal biological importance.[67]

Several authors have reported the successful use of H_2 receptor blockers in refractory anaphylactic shock.[41,68] Although H_2 receptor blockers should theoretically worsen cardiac function and increase mediator release by loss of histamine's own negative feedback inhibition, as discussed earlier, this has not been observed in clinical practice. However, until their role in shock is further established, H_2 receptor blockers are not the drugs of first choice.

USE OF STEROIDS

The role of steroids is also uncertain, as there is little evidence for any therapeutic benefit in anaphylactic shock. Even if given intravenously, they may take up to 4–6 h to be maximally effective.[8,14] Theoretical beneficial effects include an increase in tissue responsiveness to beta-adrenergic agonists, prevention of neutrophil and platelet aggregation, and inhibition of inflammatory mediator synthesis.[29,69] Steroids are believed to help prevent or shorten protracted reactions, especially those associated with bronchospasm, although there is no clear guidance as to whether standard doses of 200 mg hydrocortisone, administered intravenously at 6-h intervals, or high doses of methyl prednisolone, up to 30 mg kg^{-1}, are best.[1,3] However, oral steroid therapy is an essential part of the management of recurrent idiopathic anaphylaxis.[21,70]

MISCELLANEOUS TREATMENT

The remaining treatment modalities that have been tried in anaphylactic shock include vasopressors such as noradrenaline, dopamine and metaraminol, particularly when adrenaline and fluids have failed, although there is no conclusive data demonstrating any specific advantages in their use.[11,29,34] Glucagon is particularly recommended for patients on beta-blockers, who appear to have more frequent and severe anaphylaxis, resistant to standard adrenergic therapy.[71,72] Glucagon raises intracellular cyclic AMP by a calcium-dependent stimulation which does not involve beta-adrenergic receptors, causing positive inotropic and chronotropic cardiac effects. The recommended dose is 1 mg repeated every 5 min, followed by an infusion, although side-effects including nausea, vomiting, dizziness, hypokalaemia and blood sugar abnormalities necessitate care with its use.[73]

Finally, naloxone,[74] thyrotropin-releasing hormone[75] and the MAST suit[76,77] have all been successful, both experimentally and in occasional clinical cases.

ADMISSION AND MONITORING

Patients with significant anaphylactic reactions, including all those presenting with shock requiring adrenaline, should be admitted to a monitored intensive-care area for at least 8–12 h following resolution of symptoms, as there is a risk of both protracted and biphasic responses to anaphylaxis.[1,8,11] Biphasic responses were observed in up to 20% of patients in Stark and Sullivan's original description in 1986 of 25 consecutive cases of anaphylaxis, most frequently following oral antigen exposure or when symptoms commenced over 30 min after exposure. They noted that hypotension, laryngeal oedema or bronchospasm recurred from 1 to 8 h after an apparently symptom-free response to therapy.[78] The incidence of biphasic anaphylaxis was much lower (approximately 1%) in 276 cases of anaesthesia-related anaphylaxis reported by Fisher.[1]

THERAPY IN THE FUTURE

In the future, new experimental drugs to treat anaphylaxis, targeted specifically at the various recognized mediators of anaphylaxis, will become available. These agents may include H_3 receptor modulators,[79–81] platelet-activating factor antagonists,[82,83] leukotriene synthesis inhibitors, leukotriene antagonists, thromboxane synthetase inhibitors, neurokinin antagonists,[84] free oxygen radical scavengers,[85] nitric oxide synthesis blockers,[86] and calcium-channel-blocking drugs.[87] Hippocrates stated that 'Between wisdom and medicine there is no gulf fixed; in fact medicine possesses all the qualities that make for wisdom'.[88] Ultimately, the success of these new experimental drugs will indicate how much we actually know about anaphylactic shock, and how much we still have left to learn.

CONCLUSIONS

The three most common causes of anaphylactic fatalities are parenteral penicillin administration (100–500 deaths per year in the USA), Hymenoptera stings (40–100 deaths per year in the USA) and food-related reactions.[89] Radio-contrast media reactions (up to 500 deaths per year in the USA)[90] and aspirin or other non-steroidal anti-inflammatory drugs are the two most common causes of anaphylactoid fatalities.[91]

The diagnosis of anaphylaxis is not difficult when a patient presents with generalized urticaria, wheeze and circulatory collapse following a bee sting. However, circulatory collapse may occur rapidly in anaphylaxis without preceding skin or respiratory manifestations. There is no immediately available laboratory test to confirm the diagnosis of anaphylaxis. Serum tryptase levels are an accurate marker of mast cell degranulation that may be measured up to 6 h after the event by radioimmunoassay, but they are restricted to specialized immunology laboratories.[92] Thus, the purely clinical recognition and prompt treatment of anaphylaxis represents one of the ultimate challenges to emergency physicians in their daily practice.

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