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ANAPHYLAXIS – MANAGEMENET OF THE CRITICAL PATIENT

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INTRODUCTION

Anaphylaxis is the clinical syndrome, comprised of a constellation of features, which represents the most severe form of allergic reaction. It may be fatal and requires prompt recognition and immediate emergency intervention. Anaphylaxis results from the immunologically induced release of mast cell and basophil mediators, such as histamines and leukotrienes, after exposure to a specific antigen in previously sensitized animals; these mediators target blood vessels and smooth muscle. It has a rapid onset with multiple organ-system involvement. If medical attention is delayed, death may occur from cardiovascular collapse and/or airway obstruction. A moderate allergic reaction (angioedema) is less severe but will manifest systemically, and often affects blood vessels resulting in edema and localized swelling. Superficial systemic allergic reactions cause urticaria or wheals on the skin.

ETIOLOGY

Examples of antigens known to cause anaphylaxis include penicillins, vaccines (such as rabies, leptospriosis and parvo virus), snake venoms, food allergens (including those used in skin testing), blood and blood product transfusions, foreign proteins (insect proteins, antitoxins etc), cephalosporins, anesthetic drugs, tetracyclines, chloramphenicol, erythromycin, exogenous ACTH, TSH, insulin and oxytocin, lidocaine, salicylates, antihistamines, tranquillizers, procaine, benzocaine, iodinated contrast media, and some chemotherapeutic agents such as asparaginase. Several families of insects within the order Hymenoptera, including bees, ants, hornets, wasps, and yellow jackets, commonly cause allergic reactions in small animals. Anaphylactoid reactions are clinically indistinguishable from anaphylaxis, but are not IgE-mediated and are seen in response to radiocontrast agents and opioids acting directly on mast cells.

PATHOPHYSIOLOGY

Classic anaphylactic reactions are Type 1 hypersensitivity or allergic reactions. Type 1 hypersensitivity reactions are inflammatory reactions mediated by immunoglobulins, specifically IgE, bound to mast cells and basophils. The allergic/anaphylactic reaction results from the interaction of an allergen with specific IgE antibodies, bound to Fc receptors for IgE on mast cells and basophils. This leads to activation of mast cells and release of preformed mediators in stored granules, as well as of newly formed mediators, which are synthesized rapidly. Mediator release results in smooth muscle contraction, vasodilation, increased vascular permeability, and activation of vagal pathways, leading to the classic features of anaphylaxis, including urticaria and angioedema, bronchoconstriction and hypotension. These reactions may also be called ‘allergic reactions’. If severe and systemic they may be termed ‘anaphylaxis’.

When an antigen/allergen binds to IgE on a mast cell, there is immediate degranulation of the cell. This is mediated by an increase in cGMP levels and a decrease in cAMP levels in the cell. Preformed granules release histamine, serotonin, serine proteases, kallikreins and carboxypeptidase A. Histamine causes smooth muscle contraction and vasodilation. Heparin contributes to coagulopathy. Proteases destroy nearby cells and activate complement which leads to anaphylotoxin production. Anaphylotoxins are vasoactive substances (causing vasodilation and vascular leak). Kallikreins act on kininogens to generate kinins which are powerful vasoactive agents.

The reaction also results in the activation of cell membrane phospholipases which cause the release of arachidonic acid from cell membrane phospholipids. Arachidonic acid is a substrate for the cyclooxygenase and lipoxygenase enzymes which produce prostaglandins, prostacyclins, thromboxanes and leukotrienes. All of these substances affect vascular tone (causing vasodilation resulting in local congestion, and hypotension) and permeability (causing vascular leak which leads to local tissue edema, systemic hypovolemia and hypotension). Platelet activating factor (PAF) is also synthesized and causes platelet aggregation, serotonin release and thromboxane synthesis. Cardiovascular collapse, liver and kidney failure, sepsis and disseminated intravascular coagulation (DIC) are common sequelae.

CLINICAL SIGNS

An anaphylactic reaction is generalized and may involve multiple target organs, including skin, respiratory, gastrointestinal and cardiovascular systems. A wide variety of clinical signs may be observed: restlessness, urticaria, pruritis, angioedema (particularly swelling of the soft tissues of the head), upper airway swelling and stridor, upper airway obstruction, wheezing, bronchospasm, tachycardia, pale mucous membranes, vomiting, diarrhea, seizures or hypotensive shock.

The onset is usually sudden (within minutes to an hour after exposure to the offending antigen), and signs may last up to 24 hours. With treatment, one can expect resolution of clinical signs within hours, but a small proportion of anaphylactic reactions will follow a biphasic course (with a second phase seen in 6 to 12 hours in spite of successful initial treatment). Close monitoring of the animal for a 12-24 hour period after exposure is recommended. Should anaphylaxis recur, treatment must be reinstated a second time. Protracted anaphylaxis, which is associated with profound hypotension, may be poorly responsive, even to aggressive therapy.

If exceptionally severe, anaphylaxis may manifest as circulatory collapse, coma and death, within minutes of exposure. Circulatory collapse is related to pooling of blood in the splanchnic circulation, as well as loss of plasma volume associated with increased vascular permeability.

There are species specific reactions. In dogs, the major organ system involved in acute anaphylaxis is the liver, specifically the hepatic veins, and the gastrointestinal tract. Dogs will show initial excitement followed by vomiting, defecation, and urination. Constriction of the hepatic vein causes portal hypertension and pooling of blood in the viscera, associated with signs of shock. Bowel edema and fluid translocation also occur, resulting in diarrhea (which may be hemorrhagic). Coma, seizures, hypovolemic shock and death may occur. In cats, the major ’shock’ organs are the lung and the gastrointestinal tract. Cats show vigorous facial and head pruritis (scratching), followed by dyspnea, salivation, vomiting, incoordination and collapse. Necropsy
findings include bronchoconstriction, pulmonary hemorrhage and edema of the glottis. With insect stings, swelling at the site of the sting will be associated with systemic signs of anaphylaxis. In addition to the usual signs of anaphylaxis, massive envenomation from insect stings may cause obtundation and fever. The systemic toxic reaction to the stings may result in neurologic signs such as ataxia, facial paralysis and seizures, or in a hemorrhagic disorder with signs such as hematuria, bloody vomitus and bloody feces.

MANAGEMENT
Anaphylaxis should be considered a medical emergency, requiring immediate treatment. Parenteral epinephrine is the cornerstone of management and is the recommended first line treatment in anaphylaxis, particularly in the presence of respiratory distress or hypotension. Early administration of epinephrine has been associated with improved survival in human patients. Epinephrine has physiological benefits in the treatment of anaphylaxis: stimulation of alpha adrenoceptors increases peripheral vascular resistance thus improving blood pressure and coronary perfusion, reversing peripheral vasodilation, and decreasing angioedema. Stimulation of beta-1 adrenoceptors has both positive inotropic and chronotropic cardiac effects. Stimulation of beta-2 adrenoceptors causes bronchodilation as well as increasing intracellular cyclic adenosine monophosphate production in mast cells and basophils, thereby reducing the release of inflammatory mediators.

One must be careful to differentiate between mild, moderate or severe allergic reactions. For example, generalized angioedema and urticaria without airway involvement would not be described as anaphylaxis. A good working definition is that an anaphylactic reaction involves one or both of the two severe features: respiratory difficulty due to laryngeal edema or bronchoconstriction and hypotension (which may be associated with weakness and obtundation). Inappropriate use of epinephrine can be dangerous; most adverse events with epinephrine usage occur when it is given in overdose or as an intravenous bolus.

In the anaphylactic state, epinephrine is best administered either intramuscularly (IM) or as an intravenous (IV) constant rate infusion (CRI). Subcutaneous (SQ) administration results in a delayed onset of action and lower maximum plasma concentrations. Bolus administration of intravenous epinephrine has been associated with the induction of fatal cardiac arrhythmias and myocardial infarction. Major adverse effects occur when epinephrine is given too rapidly, inadequately diluted, or in excessive dose. Other factors existing in the anaphylactic state, such as hypoxia, acidosis, or the direct action of inflammatory mediators, may also play a role in the development of cardiovascular complications. The intravenous route should be reserved for those with unresponsive anaphylaxis; when used, electrocardiographic monitoring of the animal is recommended. The use of constant rate infusions of epinephrine somewhat reduces the risk of these adverse effects, as lower doses of epinephrine are used. For most animals, only one dose of epinephrine is needed, although repeat doses may be given at 5-15 minute intervals until hemodynamic and respiratory status improves. An alternative to repeat IM dosing of epinephrine is intravenous CRI administration.

Other supplementary therapy for anaphylaxis includes the use of H1 and H2 antihistamines such as diphenhydramine and ranitidine. While diphenhydramine has been the drug of choice for treatment of anaphylaxis in small animal patients, it is worth noting that current recommendations in human medicine are to administer these agents in combination, because H1 and H2 blockade is more effective than H1 blockade alone in preventing the symptomatology of anaphylaxis. Corticosteroids such as methylprednisolone or prednisolone may be administered intramuscularly or by slow intravenous injection. These may help prevent or minimize second-phase reactions. Phosphodiesterase inhibitors and beta-2 agonists may be beneficial to patients with bronchoconstriction. Hypotensive patients should receive intravenous fluid support with crystalloid or colloid, if necessary at ‘shock’ doses; severe cases may also require vasopressor agents such as dopamine or epinephrine. Oxygen should always be administered in any situation with respiratory or cardiovascular collapse are absent but there are other features of a systemic allergic compromise. If respiratory distress or cardiovascular collapse are absent but there are other features of a systemic allergic compromise, it is appropriate to give antihistamines and corticosteroids followed by close monitoring of the patient.

Clinically it is not possible to distinguish between anaphylaxis and anaphylactoid reactions, and treatment for both mechanisms are identical.

STEPWISE APPROACH TO THE MANAGEMENT OF ACUTE ANAPHYLAXIS:
1) Secure a patent airway and provide 100% Oxygen. Intubate and manually ventilate the patient if necessary.  
2) For cardiovascular collapse: Use Epinephrine  
   a) If peracute: 0.01 mg/kg of 1:1000 epinephrine administered IM, sublingually, endotracheally or SQ. Repeat every 15-20 minutes. If patient size is small, epinephrine can be diluted to a 1:10,000 concentration: (To prepare 1:10,000 from 1:1000 – dilute 1.0 ml of 1:1000 epinephrine (1.0mg/ml) in 9 mls of saline). The dose of I: 10,000 epinephrine is 0.1 ml/kg (0.01mg/kg). Volume in mls to be given equals body weight in kg divided by 10.  
   b) If severe reaction: administer 0.1ml/kg of 1:10,000 epinephrine IV (prepare by taking 1.0 ml of 1:1000 (1mg/ml) and dilute in 9 mls saline). Look for improvement in systemic blood pressure and perfusion parameters. If there is a poor response repeat the epinephrine administration at ½ the dose – administer this IM. If still unresponsive, move to an epinephrine CRI.  
3) Following IV catheter placement, provide an isotonic crystalloid fluid bolus at a ‘shock’ dose (90 ml/kg for dogs and 45-60 ml/kg for cats).  
4) If hypotension and hemoconcentration persist, consider adding a colloid such as Hetastarch at a dosage of 20 ml/kg rapid IV, followed by a CRI of 1-2 ml/kg/day.  
5) Use an antihistamine such as diphenhydramine at a dosage of 0.5-2.0 mg/kg IM every 8 hours as necessary.  
6) Once circulatory collapse is reversed, administer a rapidly acting steroid IV. Examples include prednisolone sodium succinate at a dosage of 8-15 mg/kg slow IV, or methylprednisolone sodium succinate at 2.0-20 mg/kg over 15-20 minutes, or dexamethasone sodium phosphate at 0-5-4.0 mg/kg IV slowly.
Steroids are not very useful during the crisis, but may control ongoing anaphylaxis due to persistent mediator release.

7) If life threatening hypotension persists, use an Epinephrine CRI: 4.0 mg epinephrine in 1 liter of saline; deliver at 1ml/kg/hr, or titrate to effect (can drip in to effect). Alternatively, a Dopamine CRI can be used at a dosage of 5-10 ug/kg/min.

8) If respiratory distress occurs, administer aminophylline at 5 mg/kg over 10 minutes, administered IV (may also be given IM). Monitor heart rate and pulse pressure. Stop if pulse pressure drops or heart rate increases. Alternative bronchodilators include Terbutaline at 0.01 mg/kg (for dogs and cats), administered subcutaneously. Upon discharge, prednisone may be dispensed at a dosage of 0.5-1 mg/kg PO every 12-24 hours for 1-2 days.

PREVENTION

The severity of previous anaphylactic reactions does not determine the severity of future reactions, and subsequent reactions could be the same, better or worse. The unpredictability depends on the degree of the allergy and the dose of allergen. With iatrogenic causes of anaphylaxis such as drug or vaccine reactions, avoidance of further exposure to those agents is essential. Blood typing and cross matching prior to blood transfusion therapy may prevent anaphylactic reactions in the recipient population.

References available from author upon request.