Anaphylaxis: From Pathophysiology to Treatment

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Allergic reactions, also known as hypersensitivity reactions, are exaggerated responses of the immune system to usually harmless substances called allergens. These hypersensitivity reactions can be localized or systemic, mild to severe, and can be life-threatening in the absence of immediate intervention. Localized allergic reactions are usually manifested by cutaneous clinical signs such as erythema, urticaria, pruritus, papules, and angioedema. Systemic hypersensitivity reactions are generally more severe, manifesting as cardiovascular, respiratory, and gastrointestinal disorders. In this presentation, we will focus on systemic hypersensitivity reactions, known as anaphylactic reactions.

Definitions and pathophysiology

Hypersensitivity reaction: "inappropriate or excessive immune response to foreign antigens".

Hypersensitivity reactions can be classified into different types.

- Type I: immediate and mediated by IgE - example: reaction to a vaccine
- Type II: mediated by cytotoxic antibodies - example: immune-mediated
- hemolytic anemia
- Type III : immune complexes - example: glomerulonephritis
- Type IV: delayed reaction mediated by T lymphocytes - example: contact dermatitis

An anaphylactic reaction (synonyms: anaphylaxis, anaphylactic shock) is a severe systemic hypersensitivity reaction, usually rapid in onset and potentially fatal, involving the release of mediators by mast cells, basophils, and inflammatory cells. Many mediators have been implicated, such as histamine, heparin, platelet-activating factor (PAF), tryptase, chymase, carboxypeptidase, proteoglycans, prostaglandins, leukotrienes, cytokines, and various chemokines. Anaphylactic reactions are thus characterized by the acute onset of clinical signs, within minutes or even hours, following exposure to a particular agent, leading to the release of various mediators. The severity of the anaphylactic reaction depends on the cellular response to the mediators released, their quantity and rate of degradation. Anaphylactic reactions are classified into different categories according to their clinical manifestation and/or pathophysiology: IgE-mediated, IgG- mediated, contact-mediated, complement-mediated, mast cell activation-mediated, response to cytokine release, and idiopathic. In fact, the term anaphylaxis is often reserved for immunological reactions, usually mediated by IgE, although immunological anaphylactic reactions can also be mediated by immune complexes, IgG, IgM, complement activation, etc. There are also anaphylactic reactions that are not immune-mediated (non-immunological reactions), and these are referred to as non-immunological anaphylactic reactions.

Etiology

Many substances and agents can lead to hypersensitivity and anaphylactic reactions. Among these, the most reported in veterinary medicine are: hymenoptera venom (bees, wasps, hornets,

ants), snake venom, antibiotics, vaccines, non-steroidal anti-inflammatory drugs, opioids, foods, blood products, imaging contrast agents, heat, cold and exercise. It should be noted that sometimes the causative agent is not identified. Indeed, in humans, the trigger is unknown in 20% of cases. This is known as idiopathic anaphylaxis.

Clinical signs

There are major differences between species as regards the main organs affected, and consequently the clinical signs observed during an anaphylactic reaction. In humans, the organs of shock are the lungs and heart; in rabbits and guinea pigs, the lungs; in rats and mice, the peripheral circulatory system; in dogs, the liver; and in cats, the lungs and respiratory tract. These differences are due to variations in the immune response, in the distribution of smooth muscle and the larger mast cell population, in the rate of antigen degradation, and in the body's reactivity to inflammatory mediators. The various signs that can be observed during an anaphylactic reaction are listed below:

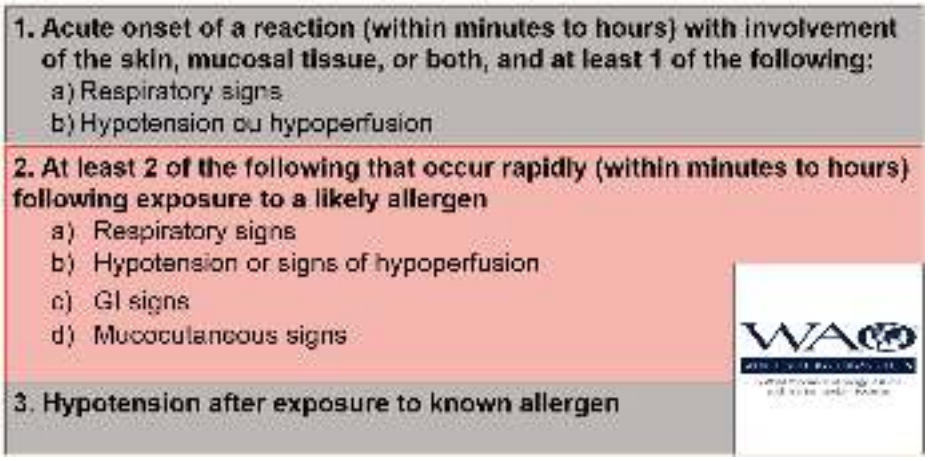
1. Skin and eye signs: erythema, urticaria, pruritus, papules, and angioedema. Conjunctival hyperemia and chemosis may also be noted. These signs are considered precursors to more severe anaphylactic reactions, but are not always present or may have a delayed onset. These signs may be subtle or severe, and generally short-lived.
2. Respiratory signs: dyspnea, stridor, bronchospasm, tachypnea, cough, wheezing. These signs are caused by pharyngeal and/or laryngeal edema, bronchoconstriction, bronchospasm, excessive mucus production in the respiratory tract, congestion and/or pulmonary hemorrhage.
3. Cardiovascular signs: hypotension, tachycardia, arrhythmias, pal or brick-red congested mucous membranes, prolonged or increased capillary refill time, decreased pulse quality, hypothermia, and altered mental status. These signs are due to peripheral vasodilation and increased vascular permeability, causing hypovolemic and distributive shock. In some cases, bradycardia rather than tachycardia is observed. due to increased vagal tone.
4. Gastrointestinal signs: vomiting, diarrhea, hemorrhagic diarrhea.

In anaphylaxis, dogs generally show signs of cardiovascular collapse, and less frequently respiratory signs. Also, hepatic venous congestion and portal hypertension are frequent, leading to digestive signs, and even hemorrhagic enteritis. In cats, respiratory and gastrointestinal signs are more common, and may be accompanied by other signs such as ptyalism, facial swelling and pruritus. The absence of cutaneous signs does not rule out an anaphylactic reaction. Indeed, in more severe anaphylactic reactions, cutaneous signs are not always present. Signs of an anaphylactic reaction usually appear rapidly, within 5 to 30 minutes after exposure to an antigen, but may sometimes be delayed by a few hours. In general, when antigen exposure is parenteral, signs appear more suddenly, progress more rapidly, and are generally more severe than when exposure is topical or cutaneous. It can be difficult to predict how an anaphylactic reaction will evolve in terms of speed of progression and severity of clinical signs, as these episodes can manifest in unusual ways. In general, the more rapidly signs develop after exposure to the antigenic substance, the more severe the reaction. Anaphylactic reactions can evolve dynamically. For example, mild clinical signs can suddenly and rapidly progress to a life-threatening reaction if aggressive care is not initiated immediately. In other cases, anaphylaxis may resolve spontaneously, without specific intervention, in a matter of minutes to hours, if there is sufficient endogenous production of mediators, such as epinephrine, angiotensin II and endothelin, to compensate for the clinical signs. Occasionally, signs may subside and disappear completely, only to reappear a few hours later. Indeed, biphasic anaphylactic reactions have been described and can occur in 1-20% of human anaphylaxis cases. There may be a delay of 1 to 72

hours between the initial signs and the signs of the second phase (more commonly 1 to 8 hours). Recurrence of clinical signs after their initial resolution may indicate a more severe, potentially fatal anaphylactic reaction. In human medicine, persistent or prolonged anaphylactic reactions have also been described, defined as reactions that last for a long time, up to 32 hours, despite treatment.

Diagnosis

Diagnosis of hypersensitivity and anaphylactic reactions is based on recent exposure to a potential antigen, such as a vaccine, drug, food or insect, and the presence of clinical signs. In human medicine, an anaphylactic reaction is likely in the presence of any of the following 3 conditions:



Several biomarkers have been studied to help diagnose anaphylactic reactions in human medicine. Among them, measurement of serum tryptase, within 3 hours of the onset of signs, is probably the most widely used test. Quantification of plasma and urine histamine is also used. The specificity of these biomarkers is generally good, but their sensitivity is much lower, making it impossible to exclude a diagnosis of anaphylaxis when their concentration is normal. Unfortunately, these tests are not readily available or well studied in veterinary medicine. However, biochemistry and abdominal ultrasound can help in the diagnosis of anaphylaxis in dogs. Indeed, a 2004 study showed that increased ALT and ultrasound changes in the gallbladder wall were associated with anaphylactic reactions. In this study, 96 dogs were divided into 2 groups: those with moderate to severe hypersensitivity signs consistent with anaphylaxis, and those with localized hypersensitivity signs or mild systemic hypersensitivity signs. Increased ALT and increased gallbladder wall thickness with alternating hypo- and hyperechoic streaks were significantly associated with anaphylaxis. The organs most affected by anaphylaxis in dogs are the liver and gastrointestinal tract. During an anaphylactic reaction, histamine is released from the gastrointestinal tract into the portal circulation. Histamine causes arterial vasodilation in the liver, resulting in a significant increase in hepatic blood flow. At venous level, however, an increase in hepatic vascular resistance is observed. These changes in hepatic blood flow, which lead to hepatic congestion and portal hypertension, can create ischemic and hypoxemic damage to hepatocytes and lead to ALT release. Alterations to the hepatic vasculature also interfere with venous drainage of the gallbladder, causing thickening of the gallbladder wall with the presence of striations. These changes are called "halo sign" or "double rim", and can, in the presence of a compatible history and clinical signs, be useful in confirming a diagnosis of anaphylaxis. Changes in the gallbladder may appear before the ALT increase, and therefore represent a very useful

biomarker. The performance of abdominal ultrasound in a potential case of anaphylaxis is of interest not only to document the gallbladder halo sign, but also to detect the presence of abdominal effusion. Indeed, the development of abdominal effusion, most often described as hemorrhagic when abdominocentesis is performed, has also been reported in several studies and case series of anaphylaxis in dogs. The pathophysiology of the hemoabdomen during anaphylaxis in humans and dogs is unclear and poorly understood. As anaphylactic reactions can lead to coagulopathy or disseminated intravascular coagulation, disorders of hemostasis may be involved in some, but not all cases. Indeed, when evaluated, clotting times and platelet counts were normal in several cases of anaphylaxis with hemoabdomen in dogs. As the amount of abdominal effusion may increase over the hours, and the development of a hemoabdomen may occur within hours of admission, it is important to repeat the ultrasound examination a few hours after the initial examination to monitor the patient, when a diagnosis of anaphylaxis is made. Following observation of an abdominal effusion, abdominocentesis should be performed to qualify the nature of the fluid, if its quantity and location allow. In the event of hemoabdomen, monitoring of hematocrit and total protein is recommended, as well as evaluation of prothrombin and activated partial thromboplastin times (PT/aPTT) and platelet count. It should be noted that if a hemoabdomen is suspected in a case of anaphylaxis, it is wise to perform coagulation time evaluation BEFORE abdominocentesis. The various tests to consider in an anaphylactic reaction therefore include: CBC (or as a minimum: PCV/PT, smear for platelet count), biochemistry (or as a minimum: ALT, glucose, creatinine and serum color assessment), PT/aPTT, abdominal ultrasound (abdominal POCUS), blood pressure assessment, pulse oximetry, ECG, and chest X-rays (or thoracic POCUS) in the presence of respiratory signs.

Treatments

Several molecules and drugs are used in the management of anaphylaxis, but few have scientifically proven efficacy, and some are controversial. Moreover, treatments for allergic and anaphylactic reactions are largely supportive, depending on the signs observed and their severity. It is important to treat anaphylaxis as quickly as possible, as it seems to respond best to treatment in its early stages. Indeed, studies have shown that late injection of epinephrine is associated with increased mortality. Table 1 shows the various treatments to be considered in the event of an anaphylactic reaction, with recommended doses.

Respiratory tract

Immediate management of a patient in anaphylactic shock involves rapid assessment of the airway and cardiovascular system (ABC triage for Airway, Breathing and Circulation). In the event of airway obstruction due to laryngeal edema, endotracheal intubation should be performed rapidly. If endotracheal tube placement is not possible, emergency tracheostomy or percutaneous cricothyrotomy should be performed rapidly. Techniques for performing these procedures are described in other texts, and the reader is invited to consult these resources as required. Oxygen therapu should be provided the event of respiratory signs and/or saturation of <95% during assessment and initial stabilization.

Fluid therapy

In the presence of hypotension, boluses of isotonic crystalloid fluid (LRS, Plasmalyte, Normosol) at doses of 10-20 ml/kg over 10 minutes (5-10 ml/kg in cats) should be administered. Once the bolus has been completed, vital signs are evaluated, and boluses are repeated if signs of shock persist. Signs of shock include: tachycardia or bradycardia, altered mental status (dullness, lethargy, very quiet or drowsy animal), increased respiratory rate, pale mucous membranes with prolonged or non-evaluable CRT or brick-red mucous membranes with rapid CRT (< 1 second),

cold extremities, decreased or non-palpable pulse, normal or decreased pressure, depending on compensatory status.

Epinephrine

Epinephrine is considered the treatment of choice for severe anaphylaxis in humans. It is the only treatment proven effective in anaphylaxis. Its beneficial effects are thought to be due to its alpha- and beta-adrenergic effects, which cause vasoconstriction to counteract the hypotension observed in anaphylaxis, as well as a reduction in mucous membrane oedema, bronchodilation, a decrease in histamine release and an increase in cardiac contractility. In humans, epinephrine is administered intramuscularly, and the injection may be repeated every 5 to 15 minutes. Most patients respond to one, two or, at most, three doses. If signs do not respond to epinephrine injections, a continuous infusion of epinephrine should be started. Sometimes, the addition of another vasopressor, such as norepinephrine, dopamine, or vasopressin, is necessary. In animals, the efficacy of intramuscular injections of epinephrine for the treatment of anaphylactic reactions is not as well documented as in human medicine, and its usefulness as a first-line treatment is controversial. In experimental studies, it has been suggested that dogs respond better to a constant intravenous infusion of epinephrine than to boluses administered intravenously or intramuscularly. Subcutaneous administration is not recommended due to potent vasoconstriction and unpredictable absorption in states of anaphylactic shock.

Bronchodilators

ß2-adrenergic agonists may be useful in the treatment of bronchoconstriction and bronchospasm observed in anaphylactic shock, when epinephrine is not sufficient. Inhaled salbutamol can help relieve signs of lower respiratory tract obstruction. However, bronchodilators do not replace epinephrine, as they do not cause vasoconstriction, and therefore do not contribute to the resolution or prevention of upper airway edema. Furthermore, there is no evidence that bronchodilators are beneficial in the treatment of anaphylactic shock. Their effects are extrapolated from their use in asthma attacks. Terbutaline, another bronchodilator from the ß2-adrenergic agonist family, can also be used intravenously or intramuscularly. Potential side effects to consider when using these molecules are tremor, tachycardia, and if overdosed, hypokalemia and hypotension.

Anti-histamines

There are 2 main categories of anti-histamines: H1 anti-histamines, such as diphenhydramine, and H2 anti-histamines, such as famotidine. H1 anti-histamines are commonly used to treat mild hypersensitivity reactions. In fact, they can help relieve cutaneous signs such as pruritus, erythema and urticaria, and ocular and nasal signs. They do not, however, relieve respiratory signs, gastrointestinal signs, or cardiovascular signs of hypotension and shock. As such, they cannot replace epinephrine. They should therefore not be used as initial treatment for anaphylactic reactions, and should not delay the administration of epinephrine. In human studies, there is no solid evidence for or against the use of H1 antihistamines to treat anaphylaxis, and so no precise recommendation can be made. They should be considered in the treatment of mild-to-moderate hypersensitivity reactions, or as an adjunct to epinephrine in the treatment of anaphylactic reactions. Similarly to H1 anti-histamines, H2 anti-histamines have no therapeutic effect in alleviating the cardiovascular and respiratory signs observed in anaphylactic reactions. Moreover, as with H1 anti-histamines, there are no human studies to support their use in anaphylaxis. However, concomitant administration of H1 and H2 anti-histamines may have a better effect in treating erythema, urticaria and other signs of hypersensitivity in humans. It is possible that this co-administration could have the same effect in animals, but this remains to be demonstrated. Finally, as with H1 anti-histamines, the administration of H2 anti-histamines should neither delay nor replace the administration of epinephrine, and should be considered in mild to

moderate hypersensitivity reactions, or as a complement to epinephrine in severe anaphylactic reactions.

Glucocorticoids

Glucocorticoids are frequently used in the treatment of all hypersensitivity reactions.It has been suggested that these drugs counteract the inflammatory cascade that occurs during hypersensitivity reactions. In general, a single dose is administered, or treatment is continued for a few days. Although glucocorticoids are widely prescribed in both human and veterinary medicine for the management of hypersensitivity cases, there are few human clinical studies and no veterinary studies evaluating their efficacy in allergic reactions or anaphylaxis, and little evidence to support their beneficial effects. The onset of glucocorticoids' anti-inflammatory effects begins a few hours after administration (4-6 hours), given their mechanism of action, which requires nuclear transcription and the creation of new molecules. As glucocorticoids require several hours to take effect, they are not at all useful in the acute treatment of anaphylaxis. Given the delay in their efficacy, another reason given for their use is to prevent the biphasic or prolonged reactions that occur in some cases of anaphylaxis. While some studies suggest that glucocorticoids are effective in preventing biphasic reactions, or at least in reducing the intensity of signs when they do occur, other studies have not supported the efficacy of glucocorticoids in reducing the likelihood of a delayed reaction. Because of the potential adverse effects of glucocorticoids and the lack of convincing evidence demonstrating their efficacy, guidelines in human medicine do not recommend their routine use in anaphylaxis. If they are used, a low dose of injectable dexamethasone or oral prednisone should be considered, bearing in mind that the onset of effects takes several hours and therefore does not alleviate acute signs.

Other

Hypoglycemia has been reported in cases of anaphylaxis. It is therefore important to measure blood glucose levels and treat hypoglycemia as needed with boluses of 50% dextrose diluted in isotonic fluid and with dextrose supplemented fluids. Applying corn syrup or other sweet liquid to the gums can help treat hypoglycemia, but note that a significant effect on blood glucose levels will only be observed after about 15 minutes. Thus, the administration of dextrose by intravenous injection is recommended for more severely hypoglycemic patients. If coagulation tests reveal coagulopathy (PT/aPTT prolonged by more than 50% of normal values), transfusion of fresh frozen plasma may be necessary. Hemoabdomen has been described in dogs, secondary to anaphylactic shock. Depending on the severity of blood loss, transfusion of packed red blood cells may be indicated. In certain cases of disseminated intravascular coagulation, transfusions of cryoprecipitate in case of fibrinogen deficiency, or platelet concentrates or lyophilized platelets in the presence of severe thrombocytopenia, are indicated.

Treatment	Dose	Comments
Endotracheal intubation Tracheostomy Cricothyrotomy	-	In case of upper respiratory tract obstruction. Propofol to facilitate intubation
Plasmalyte LRS Normosol	10 - 20 ml/kg over 10-15 minutes (dogs) 5-10 ml/kg over 10-15 minutes (cats)	For signs of distributive shock Evaluate post-bolus, repeat as necessary
Epinephrine	0.01- 0.025 mg/kg IV or IM q5-15 min 0.05 - 1 mcg/kg/min CRI	For severe cases of shock

Diphenhydramine	2 mg/kg IM or po q8-12h	For cutaneous, ocular and nasal signs. Do not administer IV Does not replace epinephrine
Famotidine	0.5 - 1 mg/kg IV or PO q12-24h	Consider in combination with anti-H1 Does not replace epinephrine
Dexamethasone	0.1 mg/kg IV/IM q24h	To consider Does not replace epinephrine
Prednisone	1 mg/kg PO q24h	To consider Does not replace epinephrine
Salbutamol (Ventolin)	1-2 inhalations q6h	In case of bronchospasm and/or bronchoconstriction Does not replace epinephrine
Norepinephrine	0.1- 2 mcg/kg/min	For hypotension refractory to fluids and epinephrine
Vasopressin	0.5-5 mU/kg/min	For hypotension refractory to fluids and epinephrine
Dopamine	5-20 mcg/kg/min	For hypotension refractory to fluids and epinephrine
Dextrose 50%	0.5-1 ml/kg IV; diluted at least 1:2 with isotonic fluid Fluids supplemented at 2.5-5% (50 - 100 ml dextrose 50% per liter of fluid)	For hypoglycemia
Fresh frozen plasma	10-20 ml/kg	When PT/aPTT > 50% prolongation
Packed red blood cell	5-10 ml/kg	If anemia and compatible clinical signs

Table 1: Treatments for anaphylactic reactions.

Prognosis

The prognosis of hypersensitivity and anaphylactic reactions depends on the agent involved, the severity of signs, the speed of treatment, and the response to therapy. The mortality rate of anaphylaxis in humans is ≤ 1% to 2% (even <0.001% in one study). In veterinary medicine, few data are available on survival rates. In a series of 61 cases of anaphylactic reactions in cats given ophthalmic antibiotics, 82% survived. In a study comparing the clinical presentation of anaphylaxis with that of sepsis in dogs, all 10 dogs with an anaphylactic reaction survived. However, the inclusion criteria that were used created a bias affecting the survival rate since animals had to survive at least 72 hours to be included in the study . A few cases of fatal anaphylactic reactions despite treatment have been described in the literature. A 2020 study published in JAVMA described mortality rates and potential prognostic factors in anaphylaxis in dogs. In this study, 67 dogs with severe anaphylactic shock were included. The diagnosis of anaphylaxis was based on the presence of acute onset clinical signs affecting at least 2 systems (integumentary, gastrointestinal, cardiovascular or respiratory) and the presence of increased ALT and/or gallbladder wall edema. The mortality rate was 14.9%. Of the 10 patients who died, 6 were

euthanized for poor prognosis or progression of clinical signs. Among the prognostic factors studied, hypothermia (<37.5°C), hyperphosphatemia, prolonged PT, concomitant increase in PT and aPTT (> 50% above the reference range), and hypoglycemia within 6 hours of admission appeared to be associated with an unfavorable outcome in these patients.

Conclusion

In many cases of hypersensitivity, the signs are mild to moderate and not life- threatening. Pruritus, erythema and a swollen muzzle are easily and quickly managed with diphenhydramine or even without treatment. Anaphylactic reactions, on the other hand, can present as medical emergencies, with severe signs that can be life-threatening. Rapid recognition and treatment are therefore imperative for the patient's survival.

References available upon request.