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HOW I TREAT . . . ANAPHYLAXIS

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INTRODUCTION

Classic anaphylaxis is caused by a patient being sensitised to an antigen and then re-encountering it once an immunologic memory has been formed. When the patient is re-exposed to the antigen, it then goes on to bind to the pre-formed IgE, which are surface bound on inflammatory cells, such as mast cells and basophils. The subsequent degranulation leads to the release of vasoactive and pro-inflammatory mediators such as histamine. There can be other forms of non-immunologic mechanisms giving rise to similar pathophysiology, and historically they were termed differently, however due to the inability to differentiate them clinically, and identical treatment, they are considered clinically as one entity.

AETIOLOGY

Sources of the anaphylaxis can be numerous and often remain unidentified. A thorough history should be taken to identify potential exposures allowing avoidance in the future. In human medicine, previous signs of hypersensitivity diseases such as atopy, asthma or food allergies, can increase the risk of severe anaphylaxis in the future. Identifying a potential antigen can allow its removal, such as an insect sting, reducing further antigen exposure, whilst also assisting with your confidence in the diagnosis.

Specific examples that may be encountered more commonly could include:

- Vaccines
- Blood products
- Iron administration parenterally
- Insect bites/stings
- Antimicrobial medications
- Radiocontrast agents
- Dietary sources

CLINICAL PRESENTATION

One of the key things about anaphylaxis is that due to the dynamic nature, it can present any number of ways and affect several body systems. There is species variation and is dependent on where mast cells are most abundant. In dogs, they are predominantly in the liver and gastrointestinal tract, whereas in cats this is the respiratory system.

Patients may present in distributive shock, as the histamine and inflammatory mediators released by the mast cells cause smooth muscle relaxation. This leads to a mass vasodilation, with a reduction in systemic blood pressure. This vasodilation may be apparent on clinical examination, typically manifesting as hyperaemic or “injected” oral mucous membranes, with a rapid capillary refill time. The absence of cold extremities and normothermia despite altered mentation and signs of shock can also be suggestive of inappropriate vascular tone.

An additional consequence of the mast cell release of histamine is altered vessel permeability. In a short space of time, there can be a significant volume lost from the intravascular space into the surrounding tissues. This loss can result in hypovolaemic shock. In contrast to the above, there may be a compensatory vasoconstriction, with the more “classic” signs of shock to include pale mucous membranes, a delayed capillary refill time, and cold extremities. As discussed below, the development of a haemoabdomen or

gastrointestinal blood loss, are possible consequences, and may contribute to hypovolaemia which may require blood product administration. Tachycardia, poor peripheral pulses, and altered mentation are common to both presentations. This is with the usual caveat that cats present in shock differently and will often be bradycardic early in the process.

Gastrointestinal signs are common in anaphylaxis, particularly in dogs. The local histamine release can lead to hepatic venous congestion, giving rise to increased pressures within the portal vein. The resultant congestion and back pressure cause fluid extravasation and gastrointestinal haemorrhage. Vomiting and diarrhoea are commonly encountered clinical signs.

Respiratory manifestations can be encountered manifesting as coughing or dyspnoea. This can be due to broncho/laryngospasm, pharyngeal oedema, pulmonary congestion or potentially the development of a pleural effusion. This may be more evident in cats than dogs.

A classic feature we often see in humans with allergic reactions is the presence of cutaneous signs. However, in retrospective studies, they were not present in 58% of anaphylactic dogs[1]. When present they can raise the suspicion for anaphylaxis, but their absence does not exclude the condition. When cutaneous signs are present, they can include urticaria, hyperaemic skin, and pruritius.

Also reported in human medicine, albeit infrequently, is a biphasic response. This is when there is an initial recovery from the anaphylactic episode, only for it to recur within the next 24 – 48 hours.

DIAGNOSIS

Unfortunately, there isn't a gold standard test to diagnose anaphylaxis, and instead relies upon pattern recognition alongside additional diagnostic features to improve diagnostic confidence.

ALT

An elevated ALT is often identified in patients with anaphylaxis.[2] With the altered blood flow, vasodilation and hypovolaemia all leading to inadequate liver perfusion and cellular damage. The liver is reliant upon the portal blood flow, and the portal hypertension reduces this. An elevated ALT was shown to have a diagnostic sensitivity of 85% and a specificity of 98%, essentially meaning a value for ALT within the reference range does not exclude anaphylaxis.

Polycythaemia

Anecdotally, we will sometimes see dogs presenting with polycythaemia. This is thought to be due to a combination of haemoconcentration secondary to a loss of plasma caused by increased vascular permeability, as well as splenic contraction in response to catecholamine release. The presence of a polycythaemia in the face of haemoperitoneum may raise concerns for anaphylaxis.

Gall bladder wall oedema

The portal vein drains blood from the gall bladder wall, and in the face of dramatic portal hypertension, there is back pressure induced thickening of the wall, giving rise to a halo appearance. This is seen as one of the earlies signs in anaphylaxis and is encountered prior to the elevation in ALT values. In a study evaluating gall bladder wall thickening, the average GB wall thickness in those with anaphylaxis was 4.7mm (CI of 4.2 – 5.2mm) compared to those with allergic disease but not anaphylaxis where the wall was 1.7mm (CI of 1.5 – 1.9mm).[2]

Haemoabdomen

Abdominal haemorrhage has been reported in several dogs with anaphylaxis.[3] The cause of this is thought to be multifactorial, with histamine having a direct anticoagulant effect, as well as the altered vessel tone and permeability. Haemostatic testing has identified prolonged clotting times, thrombocytopenia and some evidence for hyperfibrinolysis.

DIFFERENTIAL DIAGNOSES

There can be several other differentials to consider, which can present with similar signs and should be given consideration. Distributive shock can also be seen in dogs with hypoadrenocorticism, as well as a manifestation of sepsis or systemic inflammatory response syndrome. Systemic mast cell disease, or degranulation from a mast cell tumour are also possibilities that can result in similar signs. Primary liver disease, or cholangiohepatitis may give comparable imaging findings, as can a pericardial effusion with secondary tamponade.

TREATMENT

Adrenaline

Adrenaline is the mainstay of treatment and following clinical suspicion of anaphylaxis, its administration should not be delayed. Adrenaline has the benefit of counteracting the main effects of the anaphylaxis mediators, as well as stabilising mast cells to prevent ongoing degranulation.

The first line is usually the intramuscular route, with a dose of 0.01 mg/kg. The adrenaline vials are typically 1:1,000, which equates to 1 mg/ml, but this should be checked with your own formulations. This means that a dose of 0.01 ml/kg can be given IM. This is recommended to be up to a maximum of 0.3ml in dogs weighing up to 40kg, and a maximum of 0.5ml in those > 40 kg. This can be repeated every 5 – 15 minutes. However, if there is limited response, then intravenous administration should be considered.

Intravenous adrenaline boluses have not been shown to be more effective than intramuscular injections, whereas an infusion has been. A dedicated intravenous catheter, or central line, should be placed and patency confirmed to minimise the risk of extravasation of this vasoactive substance.

1 ml of 1:1,000 (1mg) of adrenaline is added to 99ml of 0.9% saline, making a 10 µg/ml solution.

The starting dose is recommended to be 0.05 µg/kg/min (3 µg/kg/hour), which equates to 0.3 ml/kg/hour. The blood pressure, and clinical perfusion parameters should be reassessed every 5 minutes, and the dosage titrated upwards as necessary. The lowest effective dose should be used, as the resultant splanchnic vasoconstriction may result in reduced gastrointestinal blood flow.

In a study in dogs, a range of 0.19 – 0.45 µg/kg/min was necessary to have a beneficial impact on cardiovascular status, which equates to 1.14 – 2.7 ml/kg/hour.[4]

Fluid therapy

Whilst the adrenaline is being administered, volume resuscitation is likely to be required. As the goal is volume replacement within the intravascular space, a balanced crystalloid such as Hartmann's should be administered as a bolus. In dogs a bolus of 10 – 20 ml/kg is administered over 10 – 15 minutes, whereas due to the lower blood volume, cats will have 5 – 10 ml/kg given. This can be repeated as necessary, reassessing their perfusion parameters and blood pressure.

Analgesia

The hepatic congestion and portal hypertension can result in pain. This may not manifest if the patient is collapsed, but the discomfort may stimulate the sympathetic tone, which can make it difficult to untangle the cause of tachycardia from that caused by shock. A full mu (µ) opioid can be selected in the initial stages, and then the need reassessed. Non-steroidal anti-inflammatory drugs should be avoided given the risk of worsening gastrointestinal injury and potential for causing an acute kidney injury in a hypoperfused patient.

Antihistamine

Antihistamines are unlikely to be of benefit with fulminant anaphylaxis, although they may help with the cutaneous sings, such as urticaria and pruritis, if present. There is a lack of evidence that pre-treatment with antihistamines reduced the risk of developing anaphylaxis.

Corticosteroids

There is limited evidence for corticosteroids in the face of anaphylaxis. Due to their mechanism of action, it

takes up to 6 hours before a clinical effect occurs. In human medicine, they have failed to identify a benefit of steroids in anaphylaxis.

PREVENTION

Knowing the trigger may assist the owner in managing the risk by avoiding the allergen if possible and help the veterinary team with identifying recurrence earlier. In some instances, there may be geographical or practical factors which may delay presentation to a vets, and in these cases having an adrenaline at home dose to administer following known exposure could be considered. There are limitations to this, such as the ability of owners to identify anaphylaxis, which as above can be difficult, particularly in the absence of dermatological lesions. EpiPens may be used, but there are the limitations of their size of needle and pre-drawn doses. In human medicine, they identified that syringes filled with 1:1,000 adrenaline solution remained stable and aseptic at 90 days. This could allow for a tailed dose to be drawn up and owners trained in injection technique, depending on the local legislation.[5]

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