Management of Anaphylaxis in an Austere or Operational Environment

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ABSTRACT

We present a case report of a Special Operations Soldier who developed anaphylaxis as a consequence of a bee sting, resulting in compromise of the operation. We review the current literature as it relates to the pathophysiology of the disease process, its diagnosis, and its management. An evidence-based field treatment algorithm is suggested.

KEYWORDS: *anaphylaxis, anaphylactic shock, epinephrine, epinephrine infusion, review, remote, austere*

Introduction

Anaphylaxis is an unpredictable emergency that requires a prompt response. It is typically precipitous, occurs in previously fit and healthy people, and can compromise a military operation or civilian expedition. It usually responds to very simple treatment with intramuscular epinephrine, but multiple doses may be required, and on rare occasions, further measures may also be required, including high-volume fluid resuscitation, additional vasopressors, and advanced airway management. We examine an operational case and provide an updated overview of the pathophysiology and optimal field management.

Case Presentation

A 34-year-old, deployed Special Operator with no prior history of anaphylaxis disturbed a wild colony of bees and was stung multiple times.

Within 4 minutes, he experienced an intensely itchy rash over his trunk and lower limbs, and he felt very lightheaded and vomited several times. He was assessed by the non–vocationally trained team medic, who diagnosed anaphylaxis. His heart rate was described as "fast," he had no palpable radial pulse, and he had a Glasgow Coma Scale score of 13 and an extensive urticarial rash. The team medic administered an intramuscular (IM) injection of 0.5mg epinephrine. His symptoms of lightheadedness and vomiting resolved. However, the rash did not improve. His radial pulse returned and a rate of 122/min was recorded. After approximately 25 minutes, the light-headedness returned and he was noted again to have an absent radial pulse. Additional epinephrine was administered via IM injection.

At this stage, the patrol commander made a decision to abandon the operation and called for a medical evacuation by rotary wing. The patient remained symptomatic and received additional IM epinephrine and 1L normal saline from the helicopter medical team. On arrival at a Tier 3 facility, he was still tachycardic and hypotensive and had an altered conscious state. He was assessed by a medical officer (specialist emergency physician) and received 2L normal saline and an epinephrine infusion with resolution of his symptoms. The infusion was discontinued after 45 minutes.

Discussion

Pathophysiology and Diagnosis

Anaphylaxis is a generalized hypersensitivity reaction, characterized by vasodilation ("flare" or erythema, distributive shock), extravasation of fluid (angioedema, hypovolemic shock), and smooth muscle contraction (bronchospasm, cramping visceral and/or uterine pain). Impaired cardiac function may also occur, although the contribution of this effect is difficult to define because of the multiple other pathophysiological changes causing hypotension. Clinically, anaphylaxis is defined as a skin rash accompanied by the involvement of at least one of the cardiovascular (e.g., low blood pressure, signs of poor perfusion, or collapse), respiratory (e.g., stridor or bronchospasm), or gastrointestinal systems (e.g., abdominal pain, vomiting, or diarrhea) following exposure to an antigen. A consensus clinical definition has been developed that can be used for both research and clinical application (Table 1).[1]

Table 1 *National Institute of Allergy and Infectious Disease/ Food Allergy and Anaphylaxis Network (NIAID/FAAN) Consensus Clinical Definition of Anaphylaxis*[1]

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), AND AT LEAST ONE OF THE FOLLOWING: a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia); b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula); b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia); c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence); d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP; b Adults: systolic BP of less than 90mmHg or greater than 30% decrease from that person's baseline

It is important to note that skin features may be absent in about 20% of cases.[2] Therefore, if an otherwise young and healthy patient presents with sudden cardiovascular collapse or severe bronchospasm, initial treatment for anaphylaxis is warranted even if the typical skin features are absent. A simple pragmatic approach to diagnosis that clinicians can use to trigger the administration of epinephrine is as follows:

*Any **acute onset illness** with **typical skin features** (urticarial rash or erythema/flushing, and/or angioedema), PLUS involvement of **respiratory** and/or **cardiovascular** systems and/or persistent severe **gastrointestinal** symptoms.*

OR

*Any **acute onset** of **hypotension** or **bronchospasm** or **upper airway obstruction** where anaphylaxis is considered possible, even if typical skin features are not present.*

It is also important to note that bradycardia typically accompanies hypotension in awake patients,[3] not tachycardia as seen in this case. Indeed, a sudden fall in heart rate after an initial tachycardia may herald impending cardiac arrest and can be triggered by inappropriately placing the patient in an upright or semi-upright (sitting) position.[4]

Causes

Overall, the causes of anaphylaxis are roughly equally distributed among drugs, stinging insect (hymenoptera) venoms, foods, and unidentified causes, although the relative proportions vary between geographical areas and populations. In urban settings, severe reactions in adults are usually due to drugs.[5] In rural and outdoor settings, severe reactions are predominantly due to hymenoptera stings (venoms), as well as other insect bites (e.g., March or "horse" flies), leech bites, snakebites, and marine venoms (e.g., jellyfish stings). Exercise may be a cofactor in some cases, leading to "summative anaphylaxis," in which a stimulus (usually a physical one such as exertion, but heat, cold, and alcohol have been suggested) appears to increase the sensitivity of mast cells to an IgE-mediated trigger in susceptible people. The main form of summative anaphylaxis is food-dependent, exercise-induced anaphylaxis, where the combination of exercise plus ingestion of the food (usually within 2 hours but sometimes as long as 5 hours) leads to sudden anaphylaxis with cardiovascular collapse during or soon after exercise. The food, despite presence of specific IgE antibodies, is normally tolerated in the absence of exercise.[6] As well as exercise being a potential cofactor in triggering some reactions, reduced physiological reserve and lactic acidosis from strenuous exercise may significantly reduce physiological reserve and thus increase the severity of any reaction and make it resistant to treatment.

Biochemical Mediators

Allergen exposure results in activation of local mast cells. These respond with degranulation and release of preformed and newly synthesized mediators. More generalized mediator release by other inflammatory cells and possibly also mast cells in areas remote from the allergen exposure then may occur, although the amplification mechanism for this process is poorly understood. [5,7]

Historically, we have focused on histamine as the main mediator involved in anaphylaxis. We now know that a wider spectrum of mediators are involved, including histamine, mast cell tryptase, tumor necrosis factor, a number of interleukins (ILs) (especially IL-6, IL-10, and tumor necrosis factor receptor inhibitor), leukotrienes, and complement breakdown products.[8] Therefore, any attempt at specific mediator antagonism is likely to be futile, and treatment relies on more general "physiological antagonism" with epinephrine and fluids to address: (i) dilation of blood vessels; (ii) extravasation of fluid into the tissues; (iii) impaired cardiac function; and

(iv) smooth muscle contraction in the lungs (bronchi) and gut.

Clinical Presentation

The individual mediators cause specific physiological effects, which, in turn, cause the signs and symptoms of anaphylaxis that we see clinically. Table 1 summarizes these clinical features.

Anaphylaxis is unique in how it produces the pattern of poor perfusion and shock seen clinically.[9] Anaphylaxis has been (and still is, in most teaching material) classified as distributive shock; however, it probably encompasses varying degrees of the four main types of shock mechanisms:

- **Cardiogenic –** from a direct myocardial depressive effect from the mediators
- **Hypovolemic –** from the loss of circulating volume into the tissues due to leaky blood vessels
- **Distributive –** from the vasodilation of vessels resulting in pooling of the circulating volume
- **Obstructive –** from vasoconstriction of the pulmonary arteries

Bradycardia may occur suddenly as a reflex response to poor venous return to the heart and a dramatic reduction in ventricular filling. There may be a reflex component to this, perhaps accentuated by anaphylactic mediators.[9] The degree to which one factor contributes to the shock pattern seen varies depending on the allergen and the route of exposure.

Management

The evidence on which management is based is extremely sparse, consisting of anecdotes, some observational studies, animal studies, pathophysiological principles, and expert opinion. The cornerstones of recommended management are epinephrine and, in presence of shock, intravenous (IV) fluid therapy.

Antihistamines

There is no evidence to support the routine use of antihistamines in anaphylaxis.[6] There have been no randomized or good observational human studies supporting the use of H1 or H2 receptor blocking drugs.[10] There is also animal evidence of harm.[11,12] H1 antihistamines, when administered parenterally, have also been associated with hypotension.[13]

The administration of oral H1 antihistamines has a role in the treatment of symptomatic itch associated with urticarial rashes seen in hypersensitivity reactions (of which anaphylaxis is a subgroup) but none as a front-line treatment agent.

Glucocorticoid Steroids

There is no evidence to support the routine use of steroids.[14] There are similarities with asthma (where there is clear evidence of benefit from steroid treatment), and it has been proposed that they have a role in attempting to shorten the duration of symptoms and reduce the incidence and severity of the biphasic response sometimes seen in anaphylaxis.[14] There is no evidence to suggest that steroids do either. We also do not know if there are any long-term effects on allergic reactivity from steroids given around the time of antigen exposure.

Field Management

The focus on the treatment of anaphylaxis in a field environment must be the placement of the patient in a supine position, the administration of epinephrine, and, if required, IV fluid resuscitation.

General Measures

It has been demonstrated that rapid changes in posture may precipitate cardiac arrest, and those who remain in a sitting position once they have lost consciousness are at greater risk of cardiac arrest. A relative bradycardia is also seen in some patients following venom-mediated anaphylaxis associated with the onset of hypotension; although the exact mechanism is not known, this may in part explain the positional cardiac arrest that is sometimes seen.[4,9] Therefore, all patients displaying evidence of anaphylaxis should be laid supine early as a basic first aid measure and should not be propped in a sitting or semi-reclined position.

Epinephrine and IV Fluids

Although there is no high-level evidence for the efficacy of epinephrine,[15] pathophysiological considerations, animal studies,[16] large case series,[17] and a prospective epinephrine infusion study, in which reaction features stopped with epinephrine and returned when the infusion was halted,[3] provide support for its likely usefulness.

The quickest and often effective route of initial administration for epinephrine is via IM administration. Absorption via this route has been shown to be superior to subcutaneous administration.[18] In most patients, a single dose is all that is required; however, in about 30% of severe reactions, repeated doses can be required.[5]

A small number of patients will not respond to IM administration—this may be due to poor circulation and hence poor absorption from muscle beds, or a need for higher systemic concentrations to reverse the cardiovascular effects of anaphylaxis. This is not infrequently seen in both hospital and pre-hospital practice and has been demonstrated in an animal model of severe anaphylaxis with cardiovascular collapse.[16] This response has been

previously described in a field environment of a patient on a jungle expedition who demonstrated resistance to repeated IM epinephrine doses.[19]

Bolus IV administration of epinephrine has historically been considered a high-risk activity and has not been recommended. It has been suggested that outside of a fully equipped resuscitation environment with monitoring facilities, IV epinephrine is not appropriate.[20]

The authors have personal experience with the use of a dilute epinephrine infusion without invasive monitoring, central line access, or a syringe driver in the place of bolus administration with no apparent loss of efficacy or increase in side effects. While this has not been subjected to a randomized trial, there is good observational evidence of efficacy and safety.[3] In an emergency out-of-hospital where there has been failure to respond to intramuscular dose(s), this option is supported by clinical guidelines produced by both the Therapeutic Guidelines group (Australia) and the Australasian Society for Clinical Immunology and Allergy.[21,22]

Fluid therapy is the second mainstay of resuscitation, after epinephrine. Large volumes of fluid may be required. The majority of patients will respond to IV fluids and epinephrine, especially where the cause is venom related, and this is most commonly seen in a field environment.[3,23]

Insertion of an IV line is now a common skill, and administration of fluid resuscitation is usually available to vocational medics or medically trained operators. It is not a complicated step to use a dilute epinephrine infusion in field settings, and any risks are likely to be acceptable if the alternative is death before medical care.

We recommend the field treatment regimen outlined in Table 2. The primary focus needs to continue to be on early IM administration of epinephrine but also recognition that there will be a small number of nonresponders who may require aggressive IV fluid resuscitation and IV epinephrine. In an operational environment, a dilute infusion can be administered safely and efficaciously and is a viable option and potentially mission saving. Unit medical officers and those involved in standard setting and education for medics should consider this as an option.

Other Measures

Some cases of very severe anaphylaxis appear to be resistant to epinephrine and fluids. Advanced procedures including intubation/ventilation, potent vasoconstrictors (e.g., vasopressin, metaraminol), and mechanical cardiac support (intra-aortic balloon pump) have been reported as necessary to prevent death. These will be outside the scope of practice for most operational units, but field medics need to be aware of these options, should evacuation to a nearby emergency center or hospital be feasible.

Table 2 *Suggested Field Management*

1. Lie patient supine if respiratory status allows.
2. Administer 0.5mg IM epinephrine (into lateral thigh, if possible).
3. Repeat 0.5mg IM if no improvement within 10 minutes.
4. Obtain IV access.
5. If systolic BP <100mmHg and/or additional signs of poor perfusion, administer 1000–2000mL of normal saline (if available).
6. If deteriorating despite IM epinephrine, consider 1:1,000,000 infusion (1mg into 1000mL normal saline or 0.5mg into 500mL or 0.25mg into 250mL): i. Administer at 1–2mL/min titrated up to achieve a clinical effect or the occurrence of side effects such as new onset tachycardia or hypertension. ii. Infusion can be increased up to "wide open" if required. Side effects with a 1:1,000,000 solution are very uncommon even when given through a wide-open line.

Summary

Anaphylaxis is a relatively common resuscitative emergency. In some patients, it can be difficult to manage with intramuscular epinephrine. The consequence is that it can be a potential operational threat and require a medical evacuation. We suggest that the field care can be optimized with the addition of a dilute epinephrine infusion for cases not responsive to intramuscular epinephrine.

Disclosures

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