

EXPERT OPINION

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Emergency management of anaphylaxis: current pharmacotherapy and future directions

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Anaphylaxis is an acute, life-threatening allergic emergency. Numerous studies have highlighted shortcomings in the emergency management of anaphylaxis, which is of considerable concern as sub-optimal immediate management increases the risk of poor outcomes. Death typically results from compromise of the cardiovascular and/or respiratory system and so emergency treatment should aim to restore blood pressure and relieve respiratory obstruction. This article provides insights on the recognition of anaphylaxis, summarises key clinically relevant insights from epidemiological investigations, and provides a state-of-the-art synopsis on the evidence-based emergency management of anaphylaxis.

Keywords: anaphylaxis, antihistamines, corticosteroids, epinephrine (adrenaline)

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1. Introduction

Anaphylaxis is an acute, life-threatening allergic emergency. Guideline-recommended treatment can improve outcomes and reduce the risk of fatality; evidence however suggests that emergency management is often sub-optimal [1]. In particular, there is a need to ensure that epinephrine (adrenaline) – which is the first-line treatment recommended in national and international guidelines – is promptly administered and that other more commonly used pharmacotherapies such as antihistamines and corticosteroids are relegated to second-line agents [2]. In this editorial, I summarise current evidence on the emergency management of anaphylaxis, highlight known shortcomings in emergency care provision and consider likely developments in pharmacotherapy and, more generally, clinical care provision [3,4].

2. Diagnosing anaphylaxis

Although there is no universally accepted definition of anaphylaxis, the definition formulated by the Resuscitation Council UK is straightforward to remember and helpful for those in the clinical frontline: “Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. This is characterised by rapidly developing life-threatening airway and/or breathing and/or circulation problems usually associated with skin and mucosal changes” [4]. The key issues highlighted by this definition are the need to recognise features indicative of respiratory and/or cardiovascular compromise, these being particularly important because fatality typically results from compromise of one or both of these organ systems [4]. It should be noted that shock is no longer a pre-requisite to diagnosing anaphylaxis, this reflecting the observation that in many reactions – especially those triggered by food(s) – there is no evidence of shock. It is also important to appreciate that the earlier distinction

between “anaphylactic” and “anaphylactoid” reactions is no longer emphasised because differences in the underlying pathophysiological mechanisms are of relatively little consequence for emergency management considerations.

3. Clinically important insights from epidemiological investigations

Epidemiological studies have provided a number of important insights into anaphylaxis, these including the observations that: reactions can occur in males and females of any age and any ethnic group; the commonest triggers are foods in children, and venom and drugs in adults; most cases of anaphylaxis are self-limiting and so, even if not treated, will spontaneously resolve; it is difficult, if not impossible, to predict which reactions will not spontaneously resolve, hence the need to treat all patients; fatality typically occurs within a few minutes to an hour of the onset of the reaction this underscoring the need for prompt treatment [5].

4. Challenges to developing a secure evidence-base for the emergency management of anaphylaxis

Treatment considerations need ideally to be informed by evidence from randomised controlled trials, as these provide the most valid evidence in relation to claims about clinical effectiveness [6]. Such trials are however difficult to execute in the context of anaphylaxis, these difficulties relating to the challenges in mounting prospective investigations in relatively uncommon emergency conditions in which only a minority of patients experience serious long-term outcomes [7]. As a result, much of the evidence-base for the management of anaphylaxis comes from studies with methodologically weak designs – case reports, case series and fatality registers, for example. There are however studies employing more robust designs that have been undertaken in healthy volunteers and patients with a history of anaphylaxis, which have been used to inform guidelines on emergency management [8-10].

5. Treatment considerations

5.1 Epinephrine is the first-line therapy

All guidelines agree that epinephrine should be considered the first-line pharmacological therapy for the emergency management of anaphylaxis [2]. This is because of its combined alpha- and beta-adrenergic properties, which: increase peripheral vasoconstriction and blood pressure; increase inotropic and chronotropic activity resulting in enhanced cardiac output; cause bronchodilation and thus helps to relieve obstruction of the lower airways; and reduce mast cell degranulation. Clinical evidence (e.g., from immunotherapy clinics and clinical challenges, where anaphylaxis is frequently seen) suggests that epinephrine begins working within seconds to minutes of administration, and case fatality studies have found that

delays in administration of epinephrine can increase the risk of fatality [11].

Epinephrine is optimally administered into the anterolateral aspect of the mid-thigh by intramuscular (i.m.) injection, from where it is rapidly absorbed [8,9]; this site has the advantages of being easily accessible and a relatively safe site for injection.

Despite clear and consistent recommendations on the administration of epinephrine as soon as possible after the onset of a reaction, evidence has consistently shown that only a minority of patients experiencing anaphylaxis actually receive treatment promptly [12]. The reasons for this are complex, but appear to include difficulties in diagnosing anaphylaxis and concerns amongst professionals about the potential dangers of epinephrine administration. Low issue rates of epinephrine auto-injectors by doctors, low carriage rates of these auto-injectors by patients, and poor training in when and how to use these auto-injectors are important barriers to optimal self-management by patients/carers [13].

The majority of patients will respond to a single dose of correctly administered epinephrine, but a minority will require one or more further injections of epinephrine. These can be given at 5 – 15 min intervals, if needed [3].

There are no absolute contraindications to the use of i.m. epinephrine in those experiencing anaphylaxis; the potential benefits and risks associated with treatment may need to be considered in those with underlying unstable cardiac disease. Transient adverse physiological effects are common, but these are generally of no long-term significance. Intravenous epinephrine may on occasions be required, but because of the increased risk of adverse events, this should, only be administered by those with relevant skills and expertise (e.g., anaesthetists) in facilities that allow careful cardiac monitoring of patients [4].

5.2 Additional emergency treatment measures

Additional emergency treatment measures that should be considered include the provision of essential life support, discontinuing any potential triggers (e.g., contrast media), high-flow oxygen, paying close attention to sudden changes in posture in order to minimise the risk of so-called “empty ventricle syndrome”, giving a bolus of fluids in those experiencing shock and inhaled/nebulised beta-2 agonists in those with persistent bronchoconstriction [3,4].

Antihistamines and corticosteroids are often used as first-line agents, but these are not life-saving and should therefore be considered as second- or third-line agents. These drugs can be helpful in relieving the cutaneous features of anaphylaxis (e.g., itch, urticaria and angioedema), and may also reduce the risk of biphasic and/or protracted reactions [14,15].

Because of the risk of biphasic reactions, patients should be monitored until symptoms have completely resolved and for a period of 6 – 12 h after recovery [16]. Following discharge, they should be warned that symptoms may recur over the following 24 h and if so they should seek urgent medical attention if such a situation arises.

5.3 Discharge arrangements and planning for subsequent longer-term care

It is important that patients are discharged with appropriate advice on how to recognise and manage any further reactions. They should be issued with an epinephrine auto-injector for the emergency self-management of further reactions [17]. Investigations will need to be undertaken to establish the trigger(s), advice on avoidance measures be provided, and consideration should, in appropriate contexts, be given to the role of immunotherapy; patients should ideally receive a personally tailored anaphylaxis management plan; these steps are best undertaken by referring the patient for a specialist allergy assessment. It is important that all relevant individuals/organisations (e.g., school-teachers) are informed of the diagnosis.

6. Future directions

The evidence-base for the management of anaphylaxis remains very weak in comparison with many other long-term conditions such as asthma and diabetes. Notwithstanding the above-described inherent challenges in developing a more secure evidence-base, there is a need to mount prospective investigations into emergency management treatments and strategies. These include, for example, improved risk stratification and the need for randomised controlled trials to establish the optimum dose of epinephrine, placebo-controlled trials of H1- and H2-antihistamines and corticosteroids to better establish their efficacy/safety profiles, and educational, psychological and organisational interventions aimed at improving acute and long-term outcomes [18,19].

There is also a need to develop greater understanding of the mechanisms underpinning anaphylaxis as this could lead to the development of more accurate diagnostic tests and also open the door to development of new therapeutic agents. Furthermore, it is important to obtain better estimates of the incidence of biphasic reactions as this could help to inform deliberations on the mandatory time period of observation following recovery from the initial reaction. Finally, there is a need for improved ways of training patients and carers to take appropriate emergency action in the context of further reactions.

7. Conclusions

Prompt treatment of patients experiencing anaphylaxis can prove life-saving. Epinephrine given through the i.m. route into the antero-lateral aspect of the mid-thigh is the treatment of choice. It is important that appropriate emergency treatment should not be delayed by administration of other agents.

Declaration of interest

A Sheikh is a member of the Resuscitation Council (UK) Guideline Committee on Anaphylaxis, the World Allergy Organization's Special Committee on Anaphylaxis, and the European Allergy and Clinical Immunology's Methodology Group for the Food Allergy and Anaphylaxis Guideline, belongs to the Royal College of General Practitioner's and has served as an advisor to ALK-Abello, Lincoln Medical, Meda and ThermoFisher.

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