



Anaphylaxis management: the essential role of adrenaline (epinephrine) auto-injectors. Should PHARMAC fund them in New Zealand?

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Abstract

Anaphylaxis is an important life-threatening medical emergency. There is extensive evidence supporting the early use of intramuscular adrenaline for first medical responders and for self-initiated treatment, in at-risk individuals. Major patient groups identified as at ongoing risk are children and adults with severe food allergy, patients with venom allergy who have not been desensitised, and those with idiopathic anaphylaxis. Individual anaphylactic events are largely unpredictable. The most effective and safe route of administration for adrenaline is intramuscular, but it is difficult for patients and carers to achieve accurate and timely self-administration using an ampoule, needle, and syringe. The adrenaline auto-injector device which is available in New Zealand (the EpiPen) is not funded by PHARMAC, and thus only available to patients and families who are able to afford the purchase cost. It is difficult to understand the continued unwillingness of PHARMAC to fund an adrenaline auto-injector device to at-risk individuals, given the large body of information supporting its efficacy and use. The Australian model, where authorisation from a relevant specialist is required, could be used.

Background

Anaphylaxis is a sudden, severe, and potentially life-threatening allergic reaction that can affect all ages. The sinister effects are on the respiratory tract and/or cardiovascular system but the skin and gut are also frequently involved. Mediator release from mast cells and basophils results in smooth muscle contraction, vasodilatation, and increased vascular permeability, leading to the classic features of anaphylaxis, including hypotension, bronchospasm, angioedema, and urticaria.^{1,2} Anaphylaxis is increasingly common³ and is considered to be under-recognised and under-reported. The prevalence of food allergy is increasing, thus suggesting that this increase in anaphylaxis is likely to continue.

Signs and symptoms vary from person to person, with onset of symptoms usually occurring within minutes of exposure, rarely commencing after more than 60 minutes. There may be rapid progression of symptoms after onset or, after initial improvement with treatment, there may be delayed deterioration one or more hours later, producing a “biphasic” reaction. In some patients, anaphylaxis will run a protracted course. The severity of an initial reaction does not necessarily predict the severity of future reactions, and the rapidity with which life-threatening reactions may develop necessitates the availability of, and early administration of, effective therapy.

Many cases of anaphylaxis are unpredictable. Data from the UK fatal anaphylaxis register shows that over two-thirds of those dying from insect sting reactions and over four-fifths of those with drug-induced anaphylaxis had no previous indication of their allergy.⁴ However the majority of those dying from food allergy had usually had previous reactions, although these had typically not been severe. Many episodes occur in the community, in the absence of a health care professional. In the UK, foods and insect stings each make up about one-quarter of deaths, the majority of the remainder being drug-related, typically anaesthetic agents and antibiotics, or idiopathic in origin. The pattern is likely to be similar in New Zealand, although detailed studies are lacking. Epidemiological studies for non-fatal anaphylaxis identify similar precipitants, but vary in relation to the prevalence of individual causes. Patients who survive anaphylaxis may be left with significant long-term disability, related to anoxic cerebral injury.

Clinical features

Symptoms occurring in fatal anaphylaxis are generally related to either shock/cardiovascular collapse, which is typically seen in reactions to intravenous drugs and insect stings, or respiratory arrest caused by intractable asthma, upper airway angioedema or both.⁵ Severe bronchospasm is a more common mode of death in food allergy than cardiovascular collapse. Additionally, death from food-induced anaphylaxis has been strongly linked with a history of asthma, though this may be only mild and infrequent.^{6,7} With foods, fatal outcome has typically occurred in patients who are aware of their food allergy and who have made reasonable efforts to avoid eating those foods.

Given the shortage of specialists in the management of allergic disease, relatively few patients receive expert advice about avoidance. Commercial catering is a particular risk for those with nut allergy. It is patients with known food or venom allergy, and those who have experienced idiopathic anaphylaxis, for whom the availability of effective self-initiated management is particularly important.

Anaphylaxis should be considered a condition where the threat of recurrence is chronic, but the event unpredictable.⁸ Appropriate management includes accurate identification of the cause, education regarding effective avoidance strategies, and appropriate medical management. This should include not only effective training and provision of self treatment, but also the effective treatment of asthma in those with food allergy and immunotherapy for those with venom allergy.⁸ Excellent results have been obtained when an appropriate management plan is put in place by a regional allergy clinic.⁹

Treatment of anaphylaxis

Injected adrenaline is widely accepted as the first-line therapy for anaphylaxis, based on its physiological effects, anecdotal evidence of efficacy, and the morbidity and mortality associated with absent or delayed administration, as documented in many studies.^{6,7,10,11} Gold and Sainsbury, for example, showed that when adrenaline was given in an outpatient setting, only 2 of 13 cases needed additional treatment in hospital, compared to 15 of 32 when it had not been used.¹⁰

It is estimated that no more than 30–40% of individuals who require adrenaline receive it. Because of lack of controlled trials, formal estimation of risk-to-benefit

ratio for the use of adrenaline is impossible—but for all major causes of anaphylaxis there is clear evidence that delays in the use of (or failure to use) adrenaline has contributed to fatal outcome and increased morbidity. For instance, in the 32 deaths from food allergy reported by Bock and colleagues, 12 did not receive adrenaline at all, 10 received it late, while 4 received it in a timely fashion.⁶ In Pumphrey's series of deaths from the UK only 14% received adrenaline prior to cardiac arrest.⁵

Although there have been concerns regarding the safety of adrenaline use, current opinion is that the benefit of appropriate doses of intramuscular (IM) adrenaline far outweighs the risk and that this is the appropriate management for first medical responders and for patient self-administration.^{12,13}

Most adverse reactions to adrenaline occur when it is given in overdose, or intravenously, as a bolus.^{5,13,14} Patients with known ischaemic heart disease are at particular risk, but appropriate use of adrenaline is not contraindicated in these patients.¹⁵ Bolus IV adrenaline is not recommended for the treatment of anaphylaxis, although adrenaline infusions may be appropriate in severe anaphylaxis in a monitored patient, for example an anaesthetic-induced reaction.¹³ Alternative treatments, such as antihistamines, corticosteroids without the use of adrenaline, or nebulised adrenaline have failed to prevent or relieve severe anaphylactic reactions.

Route of administration

A randomised, blind study in children showed the time to peak plasma adrenaline concentration was 8 ± 2 minutes after IM administration (using the EpiPen®—a self-injecting adrenaline device; DEY L.P., Napa, California; distributed in New Zealand by CSL (New Zealand) Ltd, Auckland), significantly shorter than the 34 ± 14 minutes (range 5–120) after subcutaneous injection.¹⁶ In young adults, injection in the vastus lateralis muscle in the lateral thigh gave higher plasma levels than IM injection in the deltoid region, or subcutaneous injection in the deltoid region, and thus it is the recommended site for injection.¹⁷

Adrenaline auto-injector devices provide the ability to deliver IM adrenaline at fixed doses (currently 0.3 mg, 0.15 mg). At present, it is not possible to use this device for young babies under 10 kg, as there is no fixed-dose product with less than 0.15 mg content.

The use of an adrenaline ampoule, syringe, and needle may lead to delayed dose, overdose, underdose, or no dose at all. In one study, parents (after training) took substantially longer than nurses or physicians to draw up a dose into a syringe, and the content of the parents' doses ranged 40-fold.¹⁸ For adolescents and adults to self-administer IM adrenaline using an appropriate needle and syringe is also technically difficult and has significant psychological barriers.

Reasons for delays in the use of, or lack of availability of adrenaline may be the responsibility of the physician or paramedic, the patient/caregiver or both. Failure to use adrenaline when appropriate is well documented, as is failure to prescribe for the at risk patient. If an auto-injector is prescribed and the device obtained, education in when and how to use the device is frequently lacking. A recent UK study, for example, showed that fewer than a third of patients and parents of affected children had adequate knowledge of the indications and how to use the device.¹⁹ None of the general practitioners who had prescribed for these patients personally showed the

patient how or when to use the device although the majority asked their practice nurse to do so.

The psychological and social aspects of anaphylaxis are complex, with a heavy psychological burden in patients and families of those with food allergy, with effects on quality of life shown to be greater than for children with insulin-dependent diabetes mellitus.²⁰ Both denial and risk taking play a role in risk of recurrence of anaphylaxis, with teenagers and young adults being particularly at risk.

Anaphylaxis should be considered a chronic disease, and patients ideally would be discharged from the emergency department with a prescription for an adrenaline auto-injector device, an anaphylaxis management plan, such as that available on-line from the Australasian Society for Clinical Immunology and Allergy (ASCIA website: www.allergy.org.au), education in its appropriate use and a referral to a specialist in allergy for evaluation and treatment. This applies as much to patients who are found to be at risk of anaphylaxis, as to those who have experienced anaphylaxis.

Critical role of self-injecting devices

It is unrealistic to expect any patient who is experiencing anaphylaxis to draw up and self-administer IM adrenaline in a timely and accurate way, or for family and/or caregivers to do this for a child, although this is the only option available at present for those who do not purchase an EpiPen, at the minimum cost of NZ\$120 (when ordered by the GP), or \$150–190 when obtained at a pharmacy. Many patients in New Zealand are unable to afford to buy an auto-injector, and some patients who have purchased one admit that they have been reluctant to use it because of the cost and have preferred to travel to a GP or hospital.

Compounding this situation is the inability of many patients in New Zealand to access specialist care for allergic disease because there are so few specialists in clinical immunology and allergy in New Zealand, with only one hospital-based paediatric immunologist for the entire country. Deaths from anaphylaxis are, however, relatively rare, and the provision of adrenaline auto-injectors for all at-risk individuals will be relatively costly. Risks and values are variable and uncertain, and the ethics of provision (or non-provision) of adrenaline auto-injectors complex.^{21,22}

New Zealand (like many countries in Asia, South America, and Africa) has fallen behind the UK, North America, and Australia in the provision of this treatment for individuals at risk of anaphylaxis.²³ Adrenaline auto-injectors are available under National Health Service prescription in the UK, and were made available on the Pharmaceutical Benefits Schedule in Australia from November 2003, albeit with a limit of one injector for adults and two for children, and requiring specialist recommendation. This funding followed the anaphylactic deaths of several Australian children in recent years—it will be a great sadness if such a tragedy is needed to initiate funding for EpiPens or similar devices in New Zealand.

The small community of allergy and clinical immunology specialists in New Zealand as well as Allergy New Zealand (the not-for-profit organisation which supports individuals and families affected by severe allergy disease) have campaigned on this need for New Zealanders for many years.

Disclosures: None.

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Interim response from PHARMAC: PHARMAC advises that it has not had enough time to draft a response this instance, but will do so in coming issues of the *Journal*.