ADRENALINE FOR ANAPHYLAXIS — WHAT IS THE EVIDENCE?

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ABSTRACT
International and local anaphylaxis guidelines prominently include the use of intramuscular adrenaline. However the evidence for its use is poor and the use of adrenaline in anaphylaxis is based largely on extrapolation from first principles, expert opinion and tradition. Data from basic sciences show the mechanisms of anaphylaxis are potentially amenable to therapy by adrenaline. The early use of adrenaline improves survival in animal models of anaphylaxis but delayed administration is ineffective.

Studies of fatal and near-fatal anaphylaxis in humans delineate risk factors for anaphylaxis such as pre-existing asthma, a current asthma attack, food allergies (particularly peanuts, tree nuts and shellfish), reaction to trace amounts of foods and use of non-selective β-blockers. Most reactions occur in individuals with known food allergy and with accidental ingestion. Most studies of fatal anaphylaxis show that a lack or delay in administration of adrenaline is a frequent factor in death whereas early administration of adrenaline even in severe attacks is associated with survival.

However, self-injectable adrenaline is underused even when it is available. Incorrect administration may also be an important factor, particularly with adrenaline given by needle and syringe rather than by autoinjector. Autoinjectors should be more widely available and teachers should be trained in the management of anaphylaxis and schools mandated to keep all appropriate emergency medication for named children at risk for anaphylaxis.

INTRODUCTION: ANAPHYLAXIS GUIDELINES
Up until 2007, guideline-based treatment approaches in different parts of the world were in agreement on the broad principles of management of anaphylaxis, but there were important variations in relation to the treatments to be used and the dose and route of administration of these preparations.1 Furthermore anaphylaxis guidelines were reported to be in use in only 70% of 44 responding countries polled by the World Allergy Organisation (WAO) in 2008.2 This situation was remedied in 2011 with the publication of the WOA Guidelines for the Assessment and Management of Anaphylaxis.3 This guideline focuses on the importance of a prompt clinical diagnosis and on the basic initial treatment that is urgently needed and should be available in all settings. This includes having a written emergency protocol and rehearsing it frequently, which must include promptly and simultaneously calling for help, injecting adrenaline intramuscularly and placing the patient on their back with the lower limbs elevated. Additional steps include providing high flow oxygen, maintaining the airway, establishing intravenous (IV) access and giving fluid resuscitation, and where necessary commencing cardiopulmonary resuscitation (CPR). Prevention of recurrence is given prominence with the correct identification of trigger factors and either avoidance or immunomodulation or both, as well as the provision of a patient identification disc/bracelet (e.g. MedicAlert), an action plan (Fig. 1) and patient-held emergency adrenaline, preferably via autoinjector.

Fig. 2 gives the step-by-step instructions on use of the adrenaline autoinjector.

THE USE OF ADRENALINE
In addition to this international guideline,4 the use of adrenaline is universally accepted in national anaphylaxis guidelines across the world,5,6 and in South Africa at both hospital,7,8 and primary health care level.9 However, the evidence for its use is poor and a meta-analysis of studies on adrenaline merely states that such studies have never been done.9 Conducting research is difficult when conditions are uncommon, acute in onset and short-lived. These challenges are compounded when there is no simple universally agreed upon definition and where rapid and reliable laboratory tests are not available. In addition, conducting randomised trials would be unethical and such studies have never been performed because prompt treatment with adrenaline is deemed to be critically important for survival in anaphylaxis.

Thus unavoidably the use of adrenaline in anaphylaxis is based largely on extrapolation from first principles, expert opinion and tradition, but some data do exist to strongly support the use of adrenaline from anaphylaxis, in studies of basic science, in animal model studies and in studies of fatal and near-fatal anaphylaxis.

BASIC SCIENCES
The mechanisms of anaphylaxis are well known and include markedly decreased venous tone and fluid extravasation causing reduced venous return (mixed hypovolaemic-distributive shock) as well as markedly decreased myocardial function. Aggressive fluid resuscitation is required to reverse shock, and adrenaline is given to counter these pathological mechanisms by increasing vascular tone, myocardial contractility and cardiac output.10 In a study of anaphylaxis in guinea-pig lung, histamine release could be blocked by administration of adrenaline.11 In addition, the effects of anaphylaxis on reducing ureteric peristalsis during established anaphylactic shock in dogs can be reversed by the administration of adrenaline.12

ANIMAL STUDIES
The effects of withholding treatment or of differential responses to alternative treatments cannot be conducted in humans. However animal models of...
anaphylaxis have looked at the choice of treatment of anaphylaxis and the timing of medication use, and they strongly support the early use of adrenaline. Anaphylactic shock is sometimes fatal or resistant to therapy in patients treated with propranolol, a nonselective β-adrenoceptor antagonist used in cardiovascular diseases. An animal model of anaphylaxis in rats aimed to assess the role of β₂-antagonists and used adrenaline as ‘salvage treatment’. The survival rate of the rats pre-treated with propranolol, the selective β₂-adrenoceptor antagonist ICI or adrenalectomy was significantly smaller than that with the selective 

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Fig. 1. ALLSA anaphylaxis action plan may be modified for individual patients.
\[ \beta_1 \]-adrenoceptor antagonist atenolol indicating that inhibition of \( \beta_2 \)-adrenoceptor causes more detrimental effects than that of the \( \beta_1 \)-adrenoceptor. Adrenaline prevented death 100\%, even in atenolol-pretreated rats indicating an excellent response to therapy, but merely delayed death in adrenalectomised rats, implying that a degree of endogenous adrenaline is also necessary in the response to anaphylaxis.

A further two studies of anaphylaxis in rats compared the effects of arginine vasopressin, adrenaline and terlipressin in increasing mean arterial pressure in an ovalbumin-sensitised anaesthetised anaphylactic shock rat model. In the first study, both arginine vasopressin (AVP) and adrenaline were effective but terlipressin was not. The second study randomly allocated rats to saline (no-treatment group), two boluses of adrenaline followed by continuous infusion (adrenaline group), AVP bolus followed by continuous infusion (AVP group) or adrenaline bolus followed by AVP continuous infusion (adrenaline + AVP group). In the no-treatment group and the AVP alone group no rats survived. Both the adrenaline alone group (84\% survival) and the adrenaline + AVP group (100\%) had excellent survival, indicating that adrenaline must still be considered as the first-line drug to treat anaphylactic shock.

Early administration of adrenaline is suggested for the treatment of anaphylaxis because of the belief that delayed administration of adrenaline may be ineffective because anaphylactic shock becomes refractory to treatment. An animal model of ragweed-induced anaphylaxis in dogs compared no treatment with the effects of administering adrenaline by the IV, subcutaneous (SC) and intramuscular (IM) route. This study assessed whether adrenaline is effective when given late at time of maximal hypotension. However in this circumstance adrenaline failed to cause haemodynamic recovery in fully developed canine anaphylactic shock and all the dogs died. This supports the hypothesis that anaphylaxis becomes refractory to adrenaline if treatment is given late and is in concert
with the data in studies of fatal anaphylaxis in humans showing that late administration may be futile.

STUDIES IN HUMANS OF FATAL AND NEAR-FATAL ANAPHYLAXIS

Nine large studies have been done on fatal and near-fatal anaphylaxis, 4 in the UK, (Pumphrey, 1997), (Pumphrey and Gowland, 2006) Colver et al. (2005), in the USA (Bock et al. 1997, 2002 Sampson et al. 2002) and 2 in Australia (Gold and Sainsbury, 2001, Liew et al. 2002). As most of these studies are primarily epidemiological they do help to identify high-risk groups for anaphylaxis, and some of the studies contain information that supports the use of adrenaline.

Bock et al. (1997) showed that of 32 fatal cases of anaphylaxis all but 1 were known to have food allergy before the event (and were at high risk), all but 1 had asthma (a high-risk condition for anaphylaxis in the setting of food allergy), all were accidental ingestions and most notably only 3 of the 32 were given adrenaline.

A follow-up of a further 31 subjects between 2001 and 2006 showed similar findings: all had asthma and only 4 had adrenaline administered in a timely manner.

Sampson et al. (2002) studied 13 patients with fatal and near-fatal anaphylaxis in 1992. Similar to Bock et al.’s findings, 12 of the 13 had asthma, all had food allergies and had accidental ingestions. Of the 6 who died only 2 received adrenaline in the first hour. All the patients who survived (bar 1) had adrenaline within 30 minutes of the reaction.

Gold and Sainsbury (2001) interviewed 51 parents of children with milder grades of anaphylaxis. Children had experienced on average 0.98 allergic reactions per child per year since receiving EpiPen prescription. Of these 63% were classified as anaphylaxis (but only about 16% severe anaphylaxis with loss of consciousness and perhaps a further 28% with moderate anaphylaxis in that there was fainting/dizziness). No deaths occurred, and this could not be used as an outcome measure. Children in whom the EpiPen was used were less likely to be given adrenaline in hospital and to require subsequent admission, suggesting that when used in milder grades of anaphylaxis it prevents morbidity.

Pumphrey (1999) studied 123 deaths due to anaphylaxis after studying patient folders of 164 fatalities from 1992 to 1998. All food-allergic fatal reactions caused difficulty in breathing. Food-related fatal anaphylaxis that caused difficulty in breathing was often inappropriately treated as asthma rather than anaphylaxis. Only 20% of patients given adrenaline received this before they arrested, implying that adrenaline given late is of little value in reversing established anaphylaxis, and early administration is vital.

A follow-up of a further 48 cases of fatal anaphylaxis between 2001 and 2006 showed that most had asthma and almost a third were undergoing an asthma exacerbation leading up to the fatal reaction. Over half had no professional advice related to their food allergy. Adrenaline autoinjector (EpiPen) had been provided to 40% of patients but over half of the deaths occurred in patients in whom previous reactions had been considered so mild that it was unlikely that a doctor would recommend they carry an EpiPen. Pens were used correctly by 9 subjects (19%), but 2 had time-expired and 6 may have failed to deliver an IM injection because of the depth of SC adipose tissue. Pens were used too late in the reaction by 5 subjects, were not carried on that occasion by 4 subjects and were misused by 1.

Colver et al. (2005) studied 229 cases of hospital admissions for food-allergic reactions in the UK and Ireland from 1998 to 2000. Fifty-eight cases were severe but not fatal. Three were fatal and 6 categorised as near-fatal. Of these 9 fatal and near-fatal cases, 8 had asthma and wheezing was the life-threatening symptom. Eight of the 9 (89%) had experienced a prior food-allergic reaction. Seven of 171 non-severe and 6 of 58 severe cases might have had a worse outcome if adrenaline autoinjectors had been unavailable. Six of the severe cases might have benefited if autoinjectors had been more widely prescribed.

Uguz et al. (2005) analysed self-completed questionnaire responses in the UK over a 6-month period from 109 people who had suffered severe allergic reactions. Of 126 reactions reported, 75 were in children under 16 years. Food was implicated in 112 (89%) cases. Children with asthma had more severe reactions than those without asthma, but in this study recent asthma symptoms were not associated with severity of allergic reaction reported. Self-injectable adrenaline was underused even when it was available. In only 35% of severe reactions and 13% of non-severe reactions did patients who had adrenaline administer it!

CONCLUSION

Despite the international guidelines, adrenaline is currently underutilised and often dosed suboptimally to treat anaphylaxis and is underprescribed for potential future self-administration. As of 2008, however, except for adrenaline in ampoule formulation, life-saving essentials for the assessment and management of anaphylaxis in health care settings were not universally available worldwide. Adrenaline given via needle and syringe is not an ideal treatment for anaphylaxis therapy carried by patients or parents. In experimental (non-anaphylaxis) settings parents are slower at drawing up adrenaline via a needle and syringe and the dose obtained is inaccurate, varying up to 40-fold from the intended dose. In addition to being inaccurate, parents take an average of 142 seconds +/- 13 seconds to draw up and administer adrenaline. It is likely that in stressful anaphylaxis settings even more inaccuracy and delay may be present. In South Africa all the medication polled by the WAO is available; however cost constraints mean that access to vital precautionary adrenaline autoinjector therapy is not widely available.

Substantial advocacy regarding the availability of adrenaline autoinjectors and public awareness of anaphylaxis and its treatment particularly at schools is necessary if we are to appropriately manage the burgeoning food allergy epidemic. This should include legislation from the department of education that makes it necessary for all teachers to be trained in the management of anaphylaxis and that schools be mandated to keep all appropriate emergency medication for named children at risk for anaphylaxis. Allergy clinics at state institutions should motivate to drug and therapeutic committees to have autoinjectors available to subjects at high risk of food or venom anaphylaxis.

Declaration of conflict of interest

The author declares no conflict of interest.

REFERENCES


TREATMENT OF SEVERE ANAPHYLACTIC REACTIONS
(ADULT AND CHILD)

ACUTE RESPIRATORY DIFFICULTY
(Progressive swelling, stridor, wheezing, distress)

and/or

SIGNS OF SHOCK/HYPOTENSION
(Especially if skin changes are present)

ADRENALINE
(1 mg/ml 1:1000)
>12 yrs – 0.5 ml IM
6-12 yrs – 0.3 ml IM
<6 yrs – 0.15 ml IM
Repeat every 5-15 minutes if no improvement

OXYGEN – MONITORS – IV ACCESS
• High flow oxygen
• Maintain patent airway
  (Intubate/cricothyrotomy if necessary)
• BP, Sats, ECG monitoring
• High flow IV line

PROMETHAZINE
(Antihistamine)
>12 yrs – 25 mg IM or slow IV
6-12 yrs – 12.5 mg IM or slow IV
2-6 yrs – 6.25 mg IM or slow IV
(Avoid if <2 yrs old)

CRYSTALLOID
Rapid infusion of 1-2 litres (20 ml/kg for children) if no response
to adrenaline. Repeat IV infusion as necessary, as large amounts
may be required.
Adrenaline infusion (0.1-1 μg/kg/min) ONLY if unresponsive
to IM adrenaline and fluids

NEBULISED BRONCHODILATORS
(if severe bronchospasm)
Salbutamol
>6 yrs – 5 mg every 15-20 mins
<6 yrs – 2.5 mg every 15-20 mins
WITH Ipratropium
>6 yrs – 0.5 mg every 15-20 mins
<6 yrs – 0.25 mg every 15-20 mins

GLUCAGON
(steroid)
Adult – 1-2 mg IM or slow IV every
5 mins if unresponsive to
adrenaline, and especially if on
beta-blockers
Child – 20 μg/kg (max 1 mg)
(Watch out for vomiting and
glucagonemia)

HYDROCORTISONE
>12 yrs – 200 mg IM or slow IV
6-12 yrs – 100 mg IM or slow IV
1-6 yrs – 50 mg IM or slow IV
<1 yr – 25 mg IM or slow IV

H2-RECEPTOR ANTAGONIST
Ranitidine
Adult – 50 mg IM or slow IV
(diluted in 20 ml over 2 min)
Child – 1 mg/kg (max 50 mg)
OR cimetidine
Adult – 300 mg IM or slow IV
(diluted in 20 ml over 2 min)
Child – 5 mg/kg (max 300 mg)

Management of severe anaphylaxis (Resuscitation Council of South Africa Guidelines).
Alvesco® – the small particle ICS for smaller airways

Proven Efficacy

- 0.9 µm particle size → high lung deposition in the smaller airways

Favourable safety and tolerability profile

- <1 % systemic bioavailability → cortisol suppression comparable to placebo

References: