PERSONAL PRACTICE

Management of anaphylactic reactions to food

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A 12 year old boy with eczema, asthma, and severe intolerance to cows' milk protein ate a small amount of food which contained casein. He developed a severe anaphylactic reaction, and within minutes he was dead.¹ After recent publicity of similar cases in the press, this is a scenario now greatly feared by parents of children with food intolerance. This article addresses two controversial issues, the immediate treatment of anaphylactic reactions, and the role of adrenaline for home use. The terms anaphylaxis or anaphylactic shock are used in this context to mean a severe reaction of rapid onset, with circulatory collapse and hypotension. Some have used the term anaphylaxis to describe any immediate allergic reaction mediated by IgE antibodies, however mild, but such usage fails to distinguish between a trivial event (for example, a skin test reaction) and a life threatening one. Others use the terms local anaphylaxis and systemic anaphylaxis to describe respectively local reactions (for example, acute angioedema) and generalised reactions; we confine the term anaphylaxis to the latter.

Features of anaphylactic reactions to food

Although delayed (12 hours or more) anaphylactic reactions to foods can occur,² symptoms occur within minutes after ingestion of the causative agent in almost all cases of anaphylaxis. It is often said that the sooner the symptoms occur, the more severe is the reaction, but in practice this is not a useful guide. A reaction that occurs within a minute or two of food ingestion could be very mild, moderately severe, or even fatal.

The first symptoms are often first noted in the mouth, with a sensation of burning, irritation or itching in the lips, mouth or throat, and this can provide a patient with immediate warning of a reaction to a food. In some patients the first symptom is sneezing. These early symptoms may be variably followed by feeling unwell, feeling warm, fear, generalised pruritus, and faintness. In severe cases, these early symptoms are quickly (in seconds or minutes) followed by loss of consciousness, upper airway obstruction (oedema of the larynx, epiglottis, and pharynx), lower airway obstruction (bronchoconstriction), and shock and cardiac arrhythmia.³⁻⁵ Generalised erythema progressing to urticaria, angioedema, severe bronchospasm, and conjunctivitis are all common features, but in severe cases may not

occur at all. Death may occur within minutes of ingestion of a food, and the major causes of death in anaphylaxis are obstruction to the upper airway or shock and cardiac arrhythmia.^{6,7}

Risk factors for especially severe reactions

These have been poorly documented, but can be listed as:

- History of previous severe reaction
- History of increasingly severe reaction
- History of asthma
- Certain foods: peanut, cows' milk, fish, shellfish, and egg are especially noted for their ability to provoke severe reactions, but almost any food can provoke anaphylaxis¹
- Cows' milk challenges in infants with cows' milk protein intolerance
- Treatment of atopic eczema with strict food avoidance regimens⁸
- β -Blockers: mild allergic reactions may be greatly enhanced in patients receiving β -blockers (for example, propranolol). β -Adrenergic blocking agents may potentiate anaphylactic shock and decrease the response to inhaled or injected β_2 -agonists.^{9,10}

It is unclear why some foods should be more likely than others to provoke anaphylaxis. In some cases anaphylaxis only occurs when a food is taken in conjunction with exercise. There are no studies which have prospectively studied the quantity of food required to provoke anaphylaxis, but anecdotal reports indicate that small quantities may be sufficient. In some cases, food allergens are denatured by cooking, but others are resistant to heat denaturation. It is recognised that occasionally specific food avoidance in a child with relatively mild symptoms of food intolerance is followed by anaphylactic shock when the food is reintroduced. The best known example is cows' milk protein intolerance in infancy, where it is well established that there is a clear risk of anaphylaxis during a milk challenge performed after a period of cows' milk protein avoidance.¹¹ It is for this reason that such milk challenges are often performed in hospital. It has been suggested that enhanced sensitivity is a small risk of food avoidance in a case of food intolerance,¹² and this may apply particularly to children with atopic eczema who are treated with elemental diets.^{2,8} It is unknown why in some children reactions to a food become progressively more severe with each exposure,

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whereas in others (even those with very severe reactions¹³) the reaction does not increase in intensity or even decreases with time.

Treatment of food provoked anaphylactic shock

In order of importance, the treatment is as follows.

(1) *Secure the airway* – Protection of the airway is essential, as airway obstruction is an important cause of death in anaphylaxis. Endotracheal intubation, tracheostomy, or cricothyroid puncture may be required.

(2) *Give oxygen.*

(3) *Give adrenaline* – As an α -receptor agonist, adrenaline reverses peripheral vasodilatation and reduces oedema. As a β -receptor agonist, it dilates the airways, increases the force of contraction of the heart, and suppresses histamine and leukotriene release. If cardiac arrest has not occurred, adrenaline, 0.1 ml/kg of a 1:10 000 solution ($=10 \mu\text{g/kg}$), is the most important drug. It should be given subcutaneously or intramuscularly; the latter route is certainly indicated in shock, because absorption is otherwise too slow.¹⁴ Adrenaline has a short half life, and the injection may need to be repeated. The standard advice has been to repeat at intervals of 15 to 20 minutes,¹⁵ but this may be insufficient. Therefore if a patient responds to adrenaline and then appears to be deteriorating, a further injection of the same quantity of adrenaline should be given without delay.¹⁶ If there is then no improvement after five minutes, a further injection should be given.¹⁶

If cardiac arrest has occurred, then the first priority is to establish basic life support.¹⁷ Once this has been established, adrenaline in the same dose as above ($10 \mu\text{g/kg}$) should be diluted in 10 ml saline and given intravenously (via a central vein if possible), remembering that this route carries the risk of ventricular tachycardia and fibrillation. If there is any delay in gaining intravenous access then the intraosseous route should be used. A further alternative method to give adrenaline is via an endotracheal tube. However, this route is inferior to the intravenous route, and to achieve an adequate blood concentration of adrenaline the dose is $100 \mu\text{g/kg}$.

If there is no response to the first dose of adrenaline, basic life support should continue and after three minutes a second dose should be given by the intravenous route, in a dose 10 times the first dose that is $100 \mu\text{g/kg}$. The use of sodium bicarbonate is currently recommended only when cardiac arrest has been preceded by a prolonged period of hypoxia or ischaemia, giving rise to the likelihood of the patient having a very profound acidosis. If this is considered to be the case, then an infusion of 1 mmol/kg of sodium bicarbonate may be given before the second dose of adrenaline. If the second dose of adrenaline is ineffectual, then this dose is repeated every three minutes while the patient continues to receive basic life support. However, patients where the heart has

not started after the second dose of adrenaline are unlikely to recover.

Special caution is required for patients who are receiving tricyclic antidepressants (for example, amitriptyline, imipramine), because the administration of adrenaline is associated with a grossly exaggerated response¹⁸ (for example, hypertension, cardiac arrhythmia). This is a well documented and potentially serious interaction. If adrenaline must be used then the rate and dose must be very much reduced to accommodate the exaggerated responses that will occur.

(4) *Intravenous fluids/inotropic support* – Persisting hypotension can be treated further with intravenous fluids as a 20 ml/kg bolus, with inotropic support (for example, dopamine) if there is no response.

(5) *Bronchodilators* – Administered via nebuliser, if there is bronchoconstriction.

(6) *H1 histamine antagonist* – The H1 histamine antagonist chlorpheniramine (unfortunately non-sedating antihistamines are not available for intravenous use) is administered by intramuscular or slow (add to 5 to 10 ml of sodium chloride 0.9% and give over one minute) intravenous injection in a dose of $250 \mu\text{g/kg}$ (4 weeks to 1 year), 2.5–5 mg (1 to 5 years), or 5–10 mg (6 years and above). This dose can be repeated up to four times in 24 hours over the subsequent 24 to 48 hours to prevent recurrence of urticaria.

(7) *Corticosteroids* – Corticosteroids take some hours to be effective and are unhelpful in the immediate treatment of anaphylaxis, with one important exception. This is where anaphylaxis occurs in an asthmatic who has received oral or inhaled steroids in the previous 12 months. Such patients may have some degree of adrenal atrophy¹⁹ and adrenal-pituitary axis suppression, and if this exists then additional steroid treatment (for example, intravenous hydrocortisone succinate 4 mg/kg) may be life saving. It appears that asthmatics are at increased risk for severe or fatal anaphylaxis,²⁰ and adrenal atrophy and adrenal-pituitary axis suppression is one possible explanation.

(8) *Observation for several hours* – There is a risk of relapse when the effect of antianaphylactic drugs has begun to wear off, or where there is continued absorption of the trigger food from the gastrointestinal tract.

General management following anaphylactic reaction to a food

Avoidance of the trigger food requires intelligence, a well developed sense of danger, and attention to detail. Parents need help in learning how to read and interpret the list of ingredients on food labels, and health professionals need to appreciate that lay people are unaccustomed to glancing down a list of chemical names. Many parents are unaware that casein and whey are milk proteins, or that in the UK most flour contains soya protein even though this is not declared on the label, or that a compound ingredient (for example, sausages) can be declared without mention of

the constituent ingredients. Special vigilance is required for manufactured foods which are sold unwrapped; it is impossible to be sure about the ingredients, and even when reassured by a retail outlet (for example, local baker) there is the residual worry about incorrect information and contamination of cooking utensils.^{21 22} Other potentially difficult situations are school meals (uncertainty about ingredients, difficulty arranging special meals), restaurant food and airline meals (uncertainty about ingredients), and chocolate and cocoa products (covered by separate legislation, listing of ingredients not mandatory). A special problem is posed by peanut which can occur as a concealed or undeclared ingredient in manufactured foods or restaurant meals. Examples that have led to anaphylaxis are the inclusion of peanut in almond icing,²³ dried food dressing,²⁴ Chinese food,²⁴ and vegetable burgers.²⁵ For these and many other practical problems,¹ the help of a dietitian may be invaluable. As well as educating parents and carers, it is important to educate (without frightening) the child. Even small children of 2 or 3 years can be taught to avoid certain foods, and ask, for example 'has it got egg in it?' Children can also be taught not to accept snacks and sweets offered. A Medic-Alert bracelet may be helpful.

If accidental exposure occurs, then other than adrenaline (discussed below) and the need to seek urgent advice there are two approaches worth mentioning, induced vomiting and antihistamines. Clearly an attempt to induce vomiting in a child who was in the midst of an anaphylactic reaction would carry a risk of inhalation of vomit. However, there are a few parents of children with food provoked anaphylaxis who have developed the trick, by stimulating the child's throat, of inducing vomiting immediately after ingestion of a trigger food. This is only possible where the parents immediately spot the accidental ingestion, or where immediate oral symptoms indicate that a food trigger has been ingested. We do not actually recommend induced vomiting, but it is nevertheless possible that if vomiting can be stimulated within seconds of ingestion, it may be possible to prevent the systemic absorption of most of the food. Although there is no proof that it is beneficial, it is reasonable to recommend giving an H1 receptor antagonist at the first sign of a reaction. It makes sense to supply parents with a non-sedating and quick acting agent, so the preferred drug is terfenadine; the dose, to be given twice a day, is: <3 years (not licensed) 1 mg/kg, 3–6 years 15 mg, 7–12 years 30 mg, >12 years 60 mg.

Indications for home use of adrenaline

Recent press publicity about fatal cases of food induced anaphylaxis has resulted in greater awareness of the problem and markedly enhanced anxiety for parents and doctors. One result of this, along with the ever present urge to prescribe and 'do something', has been a sudden upsurge in the supply for home use of

preloaded syringes with adrenaline. What are the indications for providing preloaded adrenaline syringes? There have been no controlled studies of adrenaline for home treatment of anaphylaxis, nor are there ever likely to be, so the recommendations made here are based on theoretical considerations, on the results of studies performed in healthy individuals, and in the light of experience encountered previously.

Current practice differs widely. Some employ adrenaline selectively, whereas others provide it where the reaction has been very mild (for example, sneezing without other symptoms). We are aware of immunology laboratories which are routinely advising the use of adrenaline syringes for any child who is found to have food specific IgE antibodies (for example, positive RAST test to peanut), regardless of the history. Many doctors are providing preloaded adrenaline syringes without training the parents in their use, which makes no sense. Our own practice is to issue adrenaline to parents only if the child has had a life threatening episode of anaphylaxis. In this context we take life threatening to mean an explosive onset of severe upper airway obstruction, severe bronchospasm and/or shock. Training of the parents, and anyone else likely to be caring for the child, is essential. Our reluctance to supply adrenaline is based on the lack of proof of lifesaving efficacy, and a number of notable drawbacks and risks. The key points are:

(1) Preloaded adrenaline syringes are potentially invasive and restrictive, the child being unable to go anywhere to play without taking the syringe and the parents ensuring that there is a fully trained adult at hand who can both judge the need for injection and have the courage to plunge a needle into someone else's child. The need to avoid certain foods is, of course, also restrictive.

(2) While some parents will be reassured by having adrenaline available, for many the possession of such equipment is associated with enhanced rather than reduced anxiety. For some, fear of the possibility of having to give an injection may be greater than fear of anaphylaxis itself.

(3) Having a preloaded syringe is plainly regarded by some (but not all) parents as a substitute for care in food avoidance, possibly increasing the overall danger to the child.

(4) There is no proof that adrenaline is life saving. The use of adrenaline does not guarantee that hypotension will be corrected, and anaphylactic shock (in some cases fatal) may be refractory to adrenaline.^{26 27} It appears that many deaths from anaphylaxis happen so rapidly that an injection of adrenaline is unlikely to be life saving. There are many reports of death occurring despite the use of adrenaline. On the other hand, for treatment with adrenaline to stand any chance of benefit, it must be given early, probably at the first sign of an allergic reaction, and adrenaline is the single most useful drug. The latter argument is our justification for supplying adrenaline for home use. The need to give the drug at the first

sign of a reaction rather than waiting for life to be visibly in danger is the reason for restricting treatment to those with a previous history of a life threatening reaction. The alternative, of supplying adrenaline to those without a history of severe reaction, risks needless injections (for example, giving the child an adrenaline injection whenever he or she sneezes a few times, just in case a trigger food has been taken), along with a number of other drawbacks listed here.

(5) There is a theoretical hazard of inadvertent intravenous injection, with the risk of arrhythmia²⁸⁻³⁰ and death.

(6) The need to eject surplus adrenaline before administration means that there is an inherent risk of overdosage, with the risk of arrhythmia²⁸⁻³⁰ and death.

(7) The use of adrenaline (for example, searching for syringe) may delay obtaining life-saving medical treatment.

(8) Where the life threatening reaction comprises severe bronchoconstriction, then adrenaline is less effective³¹ and more toxic than the use of selective β_2 -agonists (for example, nebulised salbutamol or terbutaline).

(9) Supply of preloaded syringes with adrenaline has been associated with exclusion from school in some cases. Many schools have reacted favourably and positively, especially when approached sensitively. However, some teachers have argued that it should not be their responsibility to administer injections of adrenaline, or to make the decision as to when such an injection is clinically indicated. Helpfully, some education authorities have provided indemnity for teachers in this position. Nevertheless, a few schools have taken the line that if the threat to life is so great then they are not prepared to take the responsibility for the child and exclusion has resulted. Once an entrenched position has been reached, trying to persuade schools to change their mind can be difficult, and it is vital when considering the supply of adrenaline for home use that there should be prior liaison with the community paediatric service and the school. The risk of exclusion from school has become quite widely known, with bizarre results. We have encountered cases in which the parents requested home adrenaline for the treatment of mild allergic reactions with the specific intention of having the child excluded from school. The parents were members of 'Education Otherwise', an organisation to support families who wish to practise home based education as an alternative to schooling, and further cases of this type can be expected.

A history of a previous anaphylactic reaction to a food is the most important predictor of a subsequent anaphylactic reaction. In the largest series of anaphylactic reactions to foods in children and adolescence, there were six fatal and seven near fatal cases; in all 13, there was a previous history of a serious anaphylactic reaction to food.³² Despite these data, a counter argument to the selective use of home adrenaline syringes is that potentially fatal reactions *cannot* be predicted on the basis of previous history. The argument of the

'adrenaline missionaries' is that there are very rare cases in which a fatal reaction occurs in whom previous exposure was associated with either mild symptoms or none at all. Thus a child might experience mild urticaria after eating egg, only to die of anaphylaxis the next time egg is consumed. Such cases, although atypical and rare, plainly can occur, and no doctor can guarantee otherwise. If one follows this argument to its logical conclusion, then all children who have experienced an adverse reaction to a food are at risk of death upon re-exposure to that food, and all should carry preloaded adrenaline syringes. Given the high incidence of food intolerance in childhood¹ this would result in very large numbers of children being equipped with adrenaline syringes. Our own recommendations represent an attempt to balance the relative risks of, on the one hand, a previous history of a life threatening reaction or a mild reaction, against on the other hand the various advantages and disadvantages of adrenaline syringes.

Home administration of adrenaline – practical aspects

In Britain there are currently two forms of adrenaline prefilled syringes. The first type is manufactured by International Medical Systems in Daventry, Northamptonshire and distributed by P and D Pharmaceuticals Ltd in Bordon, Hampshire. This contains adrenaline at a concentration of 1 in 1000 (1 mg in 1 ml) and sodium metabisulphite as an antioxidant. The Min-I-Jet adrenaline 1 in 1000 is available as a 1 ml disposable syringe with a 25 gauge short 0.25 inch (6.4 mm) needle for subcutaneous use. The syringe is graduated, starting at 0.2 ml (0.2 mg). In theory increments of 100 μ g above this can be given, but in practice it is not easy to be very accurate. At a dose of 10 μ g/kg, the syringe could not be used for children who weigh less than 20 kg. Since a full syringe delivers 1 mg, the parent or supervising adult has to measure the dose needed by first removing the unwanted contents, leaving the required dose for that patient. This highlights the need for a smaller syringe for children (a 0.5 ml Min-I-Jet is currently being formulated, which would allow it to be administered to a 10 kg child). Due to the unstable nature of adrenaline, the Min-I-Jet has a shelf life of nine months at 25°C (room temperature). At the time of writing, the cost of each Min-I-Jet syringe is £6.39.

The second type of prefilled syringe is the Epipen autoinjector manufactured by Allerayde in the USA. This does not have a UK product licence and is only available from Allerayde in Newark, Nottinghamshire on a named patient basis. It is designed to deliver 0.3 ml of a 1 in 1000 adrenaline injection (0.3 mg dose) subcutaneously using a spring activated concealed 0.6 inch (15 mm) needle when the pen is pushed firmly against the outer thigh. A paediatric version (Epipen Jr) contains 0.3 ml of a 1 in 2000 adrenaline injection (0.15 mg dose) to be given using a 0.5 inch (12.5 mm) needle. At a dose of 10 μ g/kg, Epipen Jr

could not be used for children who weigh less than 15 kg. Both Epipen and Epipen Jr solutions contain sodium metabisulphite as an antioxidant, and have a shelf life of approximately two years at 25°C. At the time of writing, each Epipen or Epipen Jr syringe costs £35.

If adrenaline syringes are prescribed, it is essential that parents and other carers are fully trained in their use, and this includes knowing both how and when to inject. It is irresponsible to prescribe such equipment without full instruction. Expired syringes should be kept in such a way that they could not be used in an emergency; they are useful for training purposes. It is important to emphasise that even after adrenaline is administered, medical assistance should be sought urgently, because the effects may wear off quickly and because other lifesaving treatment (for example, intravenous fluids, intubation, artificial ventilation) is likely to be required. It is reasonable for parents to have available a short acting non-sedating antihistamine (for example, terfenadine: the dose, to be given twice a day, is: <3 years (not licensed) 1 mg/kg, 3–6 years 15 mg, 7–12 years 30 mg, >12 years 60 mg).

Adrenaline inhalers

Adrenaline acid tartrate 280 µg/puff (adrenaline base 154 µg/puff) is available as a metered dose aerosol (Medihaler-Epi). About 10% of the drug reaches the lungs and is absorbed, the remainder being exhaled or deposited in the mouth and pharynx and swallowed.³³ The aerosol can be fitted into the Volumatic spacer device. In healthy individuals, large doses (15 to 30 puffs) have to be given to achieve the same plasma levels as a 300 µg subcutaneous injection^{33 34} and the recommended dose for children is 10 to 15 puffs. The patient must be able and know how to use an inhaler.

In theory, the advantages of adrenaline aerosol over subcutaneous injection³⁵ are: (a) quick absorption into the circulation and (b) possible direct effect on mucosal oedema. The disadvantages^{33 36} are: (a) more reliable, rapid, and prolonged rise of plasma adrenaline after subcutaneous injection; (b) absorption of adrenaline in the lungs may be impaired in patients with laryngeal oedema, bronchoconstriction, or bronchial mucosal oedema; and (c) studies of absorption after inhalation were performed in normal subjects who were able to perform the correct inhalation technique. It is unlikely that acutely ill children with respiratory distress could obtain as good results.

Inhaled adrenaline is not generally recommended as an alternative to injected adrenaline.^{37 38} One suggestion has been that an adrenaline inhaler may be a useful option where a school is unwilling to handle an adrenaline syringe.

Conclusions

Where a child has experienced an anaphylactic reaction to a food appropriate advice should be given to avoid the food. There remains a risk of

accidental ingestion of the food, and for those who have had a previous life threatening reaction there is a case for supplying syringes preloaded with adrenaline for use outside hospital. Parents and other responsible adults (for example, teachers) must be trained when and how to administer the injection, and there needs to be close liaison with the community paediatric service and the school. Set against the possible therapeutic advantages are a number of serious drawbacks which include the risks of overdosage, inadvertent intravenous injection, and exclusion from school.

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