Fortnightly Review

Treatment of acute anaphylaxis

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We received the letter in the box from a doctor describing how his daughter was treated during acute anaphylaxis. We considered that the issues raised were sufficiently important to be brought to the attention of doctors and we commissioned the following review article.

On the receiving end of current treatment

Last night I had the fright of my life. Our 5 year old daughter started to cough and complained of a sore throat while eating nuts (a mixture of peanut, hazel nut, walnut, and brazil nut). I looked at her throat and found nothing amiss. She then went upstairs to brush her teeth for bed, still complaining of a sore throat. Her protests on the stairs were ignored, given her renowned reputation for the "Shirley Temples." By the time she reached the bathroom, her face had broken out in acute urticaria and her tongue had became grossly (and unevenly) swollen.

I rushed her downstairs into the car. On the way to the emergency department she started to wheeze. She could hardly speak. I drove like a lunatic. I would estimate that 3-4 minutes had elapsed between ingestion of nuts and development of urticaria angio-oedema, and it was a further 5 minutes before I reached the hospital. I ran straight to the first casualty officer I saw, and told him that the child in my arms had an acute anaphylaxis and we were quickly escorted to a cubicle.

Here is where the problems started, and the following events have prompted me to write this letter. You will, of course, bear in mind that I was highly charged at this point in time. My daughter and I were left alone in the cubicle. Small delay. I shouted for oxygen, hoping to prompt some action (without being a pain in the neck). Small delay. I shouted for adrenaline (by this time not afraid to be a pain in the neck). No adrenaline forthcoming. Casualty officer fumbles through pages of a book to figure out adrenaline dosage. Second casualty officer tells the first to insert an intravenous line. Small delay while line is inserted. Child still having a lot of difficulty breathing and develops angio-oedema of the eyelids. Child complains of pains in the right knee. Pulling up the pyjama leg reveals urticaria over the joint.

Casualty officer adminsters intravenous hydrocortisone and 5 ml chlorpheniramine maleate. Child continues to wheeze. Her voice was odd, almost hoarse. There was no stridor, no cyanosis, no loss of consciousness.

I asked for an anaesthetist. More delay. Anaesthetist turns up, asks the child to cough. Good cough, anaesthetist disappears. Child's wheeze improves for a while and then starts up again. Paediatric senior house officer arrives. Talks about nebulised salbutamol. Nothing happens. Child holding her own, still wheezing. Moved to paediatric ward and eventually given nebulised salbutamol. Child survives, praise the Lord. Consultant arrives after a while and says, "Yep! This is the real McCoy all right, acute anaphylaxis, but we don't use adrenaline in children." (Maybe they said something to him in casualty about my ranting and raving.)

Fortunately, we did not have a tragedy on our hands, but I can't help thinking we were lucky. I do not wish in any way to criticise my colleagues, I am simply delighted that my daughter survived, but I think that the management of her acute anaphylaxis left something to be desired. Given the severity and the extremely rapid nature of her developing reaction, I would have thought that she should have been treated differently.

Unfortunately, cases such as the above still occur, although treatment protocols have been established. These protocols are based on an understanding of the cellular mechanisms of anaphylaxis, and they work clinically. A simple algorithm cannot be derived because the clinical syndrome of anaphylaxis is caused by different mechanisms; its onset is unpredictable; and the severity of its effects on different organ systems is variable. Randomised controlled trials of treatment are therefore not feasible and are not likely to become so. However, one of the benefits of the increase in anaphylaxis due to anaesthetic drugs which occurred in the 1970s in many countries was that patients were being monitored during anaphylaxis and some parametric observations could be added to clinical anecdote. Sufficient data were in fact collected to assess treatments.

In the absence of randomised controlled trials, therefore, treatment of anaphylaxis is based on cellular mechanisms, experiments in animals, and clinical observation. Animal experiments are least satisfactory because animals tend to react predictably, with only one organ system being affected. Clinical observations fortunately largely follow manipulations of cellular mechanisms—that is, what ought to work does work. Patients' response to treatment is, however, variable—some may recover after a simple dose of hydrocortisone and 1 litre of normal saline, although most would not. Treatments that ought not to work in theory sometimes do. Added to this, doctors' understanding of the theory behind treatment may be poor, as found by Gupta *et al* when reviewing the management of 105 anaphylactic reactions to bee stings.[1]

Variability of anaphylaxis

Anaphylaxis is an immunological description of a type I hypersensitivity reaction mediated by IgE or IgG. Conventionally, the term is used clinically to describe a variable group of symptoms that may be produced by several mechanisms. Anaphylaxis is an example of a host defence mechanism becoming hostile, similar to septic shock. Many of the same mediators play a part, but their release is more rapid and less well sustained. Histamine is an important major early mediator, but normal plasma concentrations are often

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Summary points

- Adrenaline is the treatment of choice for clinical anaphylaxis
- Volume replacement is indicated in anaphylactic cardiovascular collapse
- Follow up, diagnosis, and detailed communications are essential in preventing second reactions

obtained within minutes,[2] and other cytokines then maintain the clinical state.[3]

The term clinical anaphylaxis is used to describe a clinical state irrespective of the mechanism. It may be due to drugs, insect stings, foods, reptiles, plants, chemicals, latex, exercise, vibration, or the osmotic effects of intravenous solutions. The inhospital mortality from intravenous drugs during anaesthesia, when onset is rapid but good resuscitation facilities are available, is 4%.[4]

Anaphylactoid is used to describe reactions that are not mediated by IgE. It may also mean such a mechanism has not been proved because it has not been sought with appropriate investigations or because the investigations are limited in their specificity and sensitivity. The best assumption is that all such reactions are mediated by the immune system, so subsequent exposure to the precipitating agent should be avoided. Invalid assumptions of an anaphylactoid cause have led to fatal re-exposure.[5]

Anaphylaxis may progress slowly or rapidly. With parenteral drugs progress is usually rapid. Severity varies, and anaphylaxis may be delayed in onset for up to six hours or be biphasic, recurring in 5% of patients after clinical recovery between one hour and 72 hours after the acute event.[6]

The clinical expression of anaphylaxis is variable. The table shows the incidence of symptoms in a series of 502 patients reacting to intravenous drugs perioperatively. Cardiovascular collapse is the most common life threatening feature. Asthmatic patients will almost always develop bronchospasm. All the features may occur as a simple condition.[7]

Clinical features of anaphylaxis in 502 patients who reacted to cutaneous drugs perioperatively

	No of cases	Sole feature	Worst feature
Cardiovascular collapse	447	5	400
Bronchospasm	191	18	91
Transient	76		
From asthmatics	85		
Cutaneous symptoms:			
Rash	65		
Erythema	233		
Urticaria	42		
>1 feature	30		
Angio-oedema	125	6	17
Generalised oedema	36		
Pulmonary oedema	13	2	3
Gastrointestinal symptoms	36		

Treatment

Adrenaline is the preferred treatment. It can be given subcutaneously in mild cases and is effective intramuscularly.[8] It can be repeated every five minutes: 10% of patients who develop severe anaphylaxis outside hospital will need a repeat injection.[9] Adrenaline should be given intravenously only in severe cases and to patients who are being monitored: ventricular fibrillation may occur. The dose is shown in the box.

Waldhausen *et al* studied 49 cases of anaphylactic shock and found that adrenaline did not produce improvement or prevent shock or neurological sequelae.[10] Instead it produced severe arrhythmias or ventricular fibrillation, whereas liberal use of colloid solution reliably restored circulation and reduced airways resistance. In my study adrenaline was the drug most consistently associated with measurable improvement in blood pressure, airways resistance, and progression of angio-oedema,[7] and this is reflected in other published work. Ponten *et al* could not resuscitate two patients with fluids alone.[11] I have observed the opposite—we could not resuscitate patients with vasoconstrictors alone. Furthermore, intravenous infusion of adrenaline may not be technically possible in small children or obese patients or be available outside hospital. Steroids and antihistamines are often used, but they are rarely the preferred agents. However, steroids should be given in bronchospasm as the disease process may be longer than the time they take to work. Other vasoconstrictors (metaraminol, dopamine) are effective and may be less arrhythmogenic.[7] They have no effect on bronchospasm and their role is not established.

Mild anaphylaxis

Antihistamines or subcutaneous adrenaline may be all that is necessary if the condition is progressing slowly and not life threatening, irrespective of which organ system is affected. Under these circumstances the risks of intravenous adrenaline outweigh the benefits.

Severe anaphylaxis

The hypotension of anaphylaxis is due to vasodilatation and loss of plasma. The heart is not a primary target organ in most cases of anaphylaxis and cardiac dysfunction is usually related to underlying disease[7] or adrenaline.[12] Indeed, the cardiac effects of anaphylaxis are controversial.

The heart has histamine receptors[13] and contains drug specific IgE.[14] Isolated animal hearts and cardiac muscle preparations are adversely affected by histamine and other anaphylactic mediators.[15] In addition, some causes of the clinical syndrome of anaphylaxis such as some reactions to protamine and aggregate anaphylaxis due to protein solutions produce right ventricular failure and pulmonary hypertension.[16] However, few cases of primary cardiac failure have been described in anaphylaxis,[17] and this is partly because of the protective endogenous sympathomimetic response of the heart. Cardiac abnormalities in anaphylaxis mediated by IgE are more usually due to underlying cardiac disease or the arrhythmogenic effects of adrenaline than to the disease process itself.[7] The predominant reasons for the cardiovascular collapse are vasodilatation and leakage of plasma from capillaries with increased permeability.

The initial treatment is to give oxygen and start artificial ventilation if necessary, with external cardiac compression if the patient is pulseless. In an unmonitored patient, or when intravenous access is not available, adrenaline should be given intramuscularly

Adrenaline dosage in anaphylaxis

- Adults—0·5 ml of a 1:1000 solution intramuscularly or 3-5 ml of a 1:10 000 solution intramuscularly or slowly intravenously
- Children—0·01 ml of a 1:1000 solution per kg intramuscularly or 0·1 ml of a 1:10 000 solution per kg intravenously

The dosage is not one ampoule

or intravenously. In adults, once an intravenous line is established 1-2 litres of colloid should be given rapidly.

Colloid is more efficient and effective than crystalloid as capillaries remain leaky for longer to crystalloid than to colloid.[7 10 18] Adrenaline should be repeated and a second bolus of colloid administered. Over 90% of patients will respond to this treatment alone.

If the patient's condition is not stable adrenaline should be infused. Noradrenaline may be preferable when there is no bronchospasm,[7] and both angiotensinamide[19] and cimetidine[20 21] have been reported to improve the cardiovascular state in refractory anaphylaxis. The heart should be imaged: if it is empty and contracting well more fluid is necessary; if myocardial dysfunction is detected balloon counterpulsation may be life saving.[17]

Bronchospasm

Adrenaline and steroids should be given for bronchospasm. Other bronchodilators such as intravenous aminophylline or salbutamol by nebulisation should be considered. Most patients will improve with this treatment. Artificial ventilation should be at a slow rate to allow time for expiration and to prevent overinflation; it can be facilitated by compressing the chest during expiration.[22] Refractory bronchospasm, particularly in children, may improve with nebulised and intravenous salbutamol, and with intravenous aminophylline, isoflurane, and ketamine.[15]

Angio-oedema

Adrenaline should be given intramuscularly for angio-oedema. Antihistamines should be given as the half life of the process may be longer than the half life of adrenaline and angio-oedema may recur. Intubation may be necessary.

Pulmonary oedema

The pulmonary oedema of anaphylaxis is a membrane oedema and associated with a volume deficit. The treatment is (*a*) to use positive and expiratory pressure to the point when oedema is no longer visible in the tubing of the breathing circuit and (*b*) to cautiously fill the patient with colloid. As long as oxygenation is improving during infusion of colloid the treatment is appropriate. Diuretics are contraindicated as they make the volume deficit worse.

Occasionally a fulminant pulmonary oedema lasting up to 24 hours occurs, with massive losses of fluid.[23] The use of positive end expiratory pressure to control the fluid leakage may rarely lead to loss of fluid through the lung surface and require thoracotomy to prevent tamponade. This variant is usually seen at the end of bypass and attributed to (but not proved due to) protamine or protein solutions.[24 25]

Follow up

The treatment of acute anaphylaxis does not end with the acute episode. The cause of the reaction should be determined when possible. The history is of vital importance and a history of previous exposure of little value.[5] Cutaneous testing and radioimmunoassays for specific IgE should be carried out. The findings should be clearly documented and explained to the patient. Patients should be instructed to carry a letter at all times in addition to wearing a warning device. The letter is a vital adjunct to a warning bracelet or necklace because it gives subsequent practitioners the opportunity to assess the evidence for the accuracy of the warning device. Patients or parents of patients at risk of reactions to foods, environmental allergens, chemicals, or plants during inadvertent exposure should be told how to treat themselves or their child with injectable or inhaled adrenaline.[26] Patients with recurrent anaphylaxis of unknown cause should be treated with steroids.[27] Desensitisation should be considered when possible. Pretreatment with antihistamines, sympathomimetics, and steroids may be effective in preventing second reactions under some circumstances such as reactions to intravenous contrast media.[28 29]

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