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Preventing and Managing Drug-Induced Anaphylaxis

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Abstract

Drug-induced anaphylaxis and anaphylactoid reactions have increased in frequency with more widespread use of pharmaceutical agents. Anaphylaxis is a systemic, severe immediate hypersensitivity reaction caused by immunoglobulin (Ig) E-mediated immunological release of mediators of mast cells and basophils. An anaphylactoid reaction is an event similar to anaphylaxis but is not mediated by IgE.

The incidence of anaphylactic or anaphylactoid reactions differs amongst classes of medications. Antibacterials are the most usual offenders, and penicillins are the most studied. Other compounds commonly causing reactions include nonsteroidal anti-inflammatory drugs, anaesthetics, muscle relaxants, latex and radiocontrast media.

Prevention, if possible, is the purpose of detailed patient history taking and physical examination. Simple strategies can be employed to decrease the risk of anaphylaxis. These include consideration of the route of drug administration, identification of patients with known causes of anaphylaxis, and the knowledge that certain medications cross react and are contraindicated in those with known history of anaphylaxis. Tests are available, and include IgE-specific skin tests and radioallergosorbent tests. Penicillins are the only compounds whose antigenic determinants are well documented, it is therefore difficult to determine the negative predictive value of other compounds tested. Oral challenge remains an alternative, though entails risk. Desensitisation procedures, as well as gradual dose escalation protocols, are available and can be implemented based on patient history and diagnostic testing.

The management of anaphylaxis is based on control of the airway, breathing and circulation. Treatment consists of epinephrine (adrenaline) and supportive measures. Rapid diagnosis and intervention are important in these life-threatening reactions. After stabilisation, all individuals with a documented history of anaphylaxis require a Medic-Alert bracelet or necklace, and an identification card for their wallet or purse.

Since before the time of kings and pharaohs, anaphylaxis has mystified generations. As early as 2641BC there was evidence of an unexplained death due to airway obstruction and irreversible vascular collapse.[1] The term anaphylaxis was coined by Portier and Richet in 1902.[2] Drug-induced anaphylaxis has become a problem with the widespread use of novel pharmaceutical agents within the past 60 years. These medications have provided new therapies to cure and control many diseases that previously had caused considerable morbidity and mortality, but there has been a cost. The advent of these new agents has resulted in an increase in the severity and incidence of adverse drug reactions. Pencillin is an example of a lifesaving drug that has been found to cause 1 case of anaphylaxis for every 10 000 courses of therapy.[3] These numbers are formidable considering that one managed care organisation's prescription plan records found that, of the 1 699 074 oral antibacterial prescriptions written over a 1-year period, 870 610 were for a penicillin antibacterial.[4] In this group, 87 cases of anaphylaxis due to penicillin would be expected.

1. Definition and Mechanisms

Anaphylaxis is a systemic, immediate hypersensitivity reaction caused by immunoglobulin (Ig) E-mediated immunological release of mediators of mast cells and basophils.[5] The mast cell has a Fc receptor on its surface that binds IgE. An individual previously exposed to an offending antigen produces specific IgE. Upon re-exposure, if the IgE antibody has reached high enough levels, it will activate the mast cell and cause release of its vasoactive contents. The mediators released include histamine, the leukotrienes C4, D4, and E4, eosinophil chemotactic factor of anaphylaxis, neutrophil chemotactic factor of anaphylaxis, the mast cell marker tryptase and platelet activating factor. These factors have many systemic effects including smooth muscle spasm, bronchospasm, increased capillary leak and mucosal oedema and inflammation. The clinical manifestations can involve any organ system, but are mainly seen in the cutaneous, respiratory, gastrointestinal and cardiovascular systems. Classic signs and symptoms include, but are not limited to, urticaria and angioedema, dyspnoea, wheezing, upper airway oedema, dizziness, hypotension and shock, nausea, vomiting, crampy abdominal pain, flushing, headache and substernal chest pain.[2,6] Anaphylaxis is a medical emergency requiring immediate attention or death may ensue. It is also important to remember that mast cells release mediators hours after the initial reaction causing the biphasic or late phase reaction of anaphylaxis.

The mast cell can be activated by means other than IgE. These mechanisms include other immunological and non-immunological provocations. Complement-mediated anaphylatoxins are formed when IgG aggregates from intravenous immunoglobulin, causing an anaphylactic picture in those with this type of response to the immunoglobulin.[7] A similar reaction may occur when antibodies are created to mismatched red blood cells during blood transfusions. Non-immune mechanisms cause direct release of vasoactive substances from the mast cells. Medications such as opioids, aspirin (acetylsalicylic acid), radiocontrast media, dextrans and neuromuscular blocking agents have been found to directly stimulate mast cells.[7]

The symptoms of anaphylaxis and anaphylactoid reactions are at times misinterpreted, which may lead to improper treatment. The differential diagnosis of anaphylaxis and anaphylactoid reactions is summarised in table I.

Table I. Differential diagnosis of anaphylaxis and anaphylactoid reactions (reproduced from Lieberman,[5] with permission)

Anaphylaxis and anaphylactoid reactions
to exogenously administered agents
to physical factors
exercise
cold, heat, sunlight
idiopathic
Vasodepressor reactions
Flush syndromes
carcinoid
postmenopausal
chlorpropamide alcohol
medullary carcinoma thyroid
autonomic epilepsy
'Restaurant syndromes'
monosodium glutamate (MSG)
sulfites
scrombroidosis
Other forms of shock
haemorrhagic
cardiogenic
endotoxic
Excess endogenous production of histamine syndromes
systemic mastocytosis
urticaria pigmentosa
basophilic leukaemia
acute promyelocytic leukaemia (tretinoin treatment)
hydatid cyst
Nonorganic disease
panic attacks
Munchausen's stridor
vocal chord dysfunction syndrome
globus hystericus
undifferentiated somatoform anaphylaxis
Miscellaneous
hereditary angioedema
'progesterone' anaphylaxis
urticarial vasculitis
phaeochromocytoma
hyperimmunoglobulin E, urticaria syndrome
neurological (seizures, stroke)
pseudoanaphylaxis
red man syndrome (vancomycin)
capillary leak syndrome

2. Incidence

The exact incidence of drug-induced anaphylaxis is unknown. The Boston Collaborative Drug Surveillance Program tried to answer this question. In 1973, they found 6 drug reactions and 0.87 deaths per 10 000 patients studied.[8] Four years later they reported drug-induced anaphylaxis in 12 of 32 812 monitored patients on selected medical wards. This reflected an incidence of 0.04%.[9] In 1990, a review of patients admitted to a university hospital noted 9 patients with anaphylaxis of out of a total of 20 064 admissions. The causes of anaphylaxis were predominantly drug related, but food and stinging insect reactions were also included. Again an incidence of 0.04% was recorded.[10] A report using data from emergency rescue teams in Munich, Germany found the rate of anaphylaxis to be 9.79 per 100 000 individuals or 0.01%.[11] Klein and Yocum[12] noted the incidence of anaphylaxis to be 0.09% as determined by a chart review of 19 122 patients seen at the Emergency Department in Rochester, Minnesota, US during a 4-month period. In another study by Yocum et al.,[13] the annual incidence of anaphylaxis was 21 per 100 000 individuals per year, with a fatality rate of 0.65% during the 5-year period. Causes of the anaphylactic reactions were medications, foods and insect stings.

The incidence of anaphylactic or anaphylactoid reactions varies amongst different classes of medications. Antibacterials are the most common class of medications to produce anaphylactic or anaphylactoid reactions. Penicillin is the most studied. The rate of anaphylactic or anaphylactoid reactions is 1 to 5 per 10 000 patient courses of treatment.[14] The rate of fatal anaphylaxis from penicillin has been shown to be 0.002%, and this drug accounts for 75% of all fatal anaphylactic episodes in the US each year.[15] The incidence of anaphylactoid reactions to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) varies greatly depending on who is included in the study population. The incidence was 2% in a questionnaire-based study of children and 97% in a study of adults with concomitant asthma, rhinosinusitis and nasal polyps.[16,17] To clarify the prevalence of anaphylactoid reactions to aspirin and other NSAIDs, a study of 51 797 patients taking these medications was initiated. In

this group there were 35 cases of shock, 11 cases of angioedema and 106 cases of urticaria.[18] In other studies, including one of 808 non-atopic individuals, 7 such individuals (0.9%) reported an anaphylactoid episode after ingesting aspirin.[19] In another series of patients with anaphylaxis, aspirin was a frequent offender accounting for approximately 3% of all events.[20]

Many anaesthetic medications can cause anaphylactic or anaphylactoid reactions. The largest studies have been conducted in France, where the incidence of intraoperative anaphylactic reactions was been found to be 1 in 6000. When taking into consideration all immediate reactions (both anaphylactic and anaphylactoid), the incidence was 1 in 3500.[21] A recent survey completed in 27 centres found that the cause of shock could be determined by radioimmunoassay of serum in 57.8% of the patients investigated. 59% of the time the aetiological agent causing the reaction was muscle relaxants. Implicated agents include suxamethonium chloride, vecuronium bromide, pancuronium bromide, alcuronium bromide or chloride, atracurium besilate and gallamine triethiodide.[22] Similar results were seen in studies done in Australia, Great Britain, the US and Canada.[23] Hypnosedatives and opioids, including morphinomimetics, antipsychotics and benzodiazepines, have also been found to cause anaphylactoid reactions.

Local anaesthetics may cause allergic reactions. A metabolite of the ester local anaesthetics, *para*-aminobenzoic acid, has been found to be allergenic.[24] This highly antigenic substance is thought to be the source for reactions attributed to the ester class of local anaesthetic agents which includes benzocaine, cocaine, procaine, propoxycaine and tetracaine. Methylparaben, a preservative and bacteriostatic agent found in many older local anaesthetic preparations, other drugs, foods and cosmetics, is related to aminobenzoic acid and has allergenic properties. Currently it has been taken out of local anaesthetic cartridges, but is still found in multidose vials. Another preservative used, which is also allergenic, is sodium bisulfite (metabisulfite). Anaphylaxis to sodium bisulfite has been reported.[24] Finally, hypersensitivity reactions to preservative-free amide local anaesthetics have been reported, but are rare. True immunological reactions to local anaesthetics are rare, making up less than 1% of all adverse reactions to local anaesthetics.[25]

Latex exposure can cause anaphylaxis in an increasing number of patients. Reactions were uncommon until the 1980s with the introduction of universal precautions and the use of latex gloves to protect against the spread of infectious diseases. Healthcare workers and patients exposed to multiple surgical procedures are at greatest risk for latex sensitivity. The rate of sensitivity is estimated to be as high as 36% in atopic, frequently exposed workers.[26] In patients with spina bifida, the incidence of sensitisation ranges from 18 to 73%.[27] Studies of blood donors have shown that 6% have measurable anti-latex IgE.[28]

Radiocontrast media reactions have decreased with the introduction of lower osmolar agents. Older agents caused reactions in approximately 1% of patients, with a fatality rate of 0.009%. Reactions are reported to occur in 0.04% of patients receiving lower osmolar preparations.[29] Patients with a history of contrast media reactions can receive contrast again with pretreatment and use of a low molecular weight contrast. Various pretreatment regimes have been described.[30]

3. Prevention of Anaphylaxis

3.1 Patient History and Physical Examination

Unfortunately, anaphylactic reactions to medications often can not be predicted. A thorough patient history and physical examination can decrease the number of reactions by allowing precautions to be implemented. A clinician with knowledge of the immunological and biochemical cross reactivity between medications can often foresee and prevent imprudent drug choices. Cross reactivity exists amongst β-lactam antibacterials. A study of β-lactam antibacterials by Adkinson[31] found that cross reactivity was predictable and nearly complete across semi-synthetic penicillins, partial and incomplete across β-lactams with 2 nuclear rings

and negligible across monobactams. Cross reactivity also exists between local anaesthetics. Any ester or amide local anaesthetic containing the preservative methylparaben may cause reactions. Ester local anaesthetics may cross react and if there is a reaction, another class of anaesthetic should be used. Amide anaesthetics, although only noted in a handful of case reports,[24] can also cross react. The clinician has an important role in determining whether the history of a reaction can be classified as a true IgE-mediated allergic reaction from the medication.

History of 'drug allergy' may not be a good indicator of true immunological reaction. Up to 10% of the outpatient population will report a history of penicillin allergy.[32] About 80 to 95% of patients with a history of penicillin allergy have a negative penicillin skin test.[33] Patient examination at the time of reaction has been found to be a more accurate predictor of true allergic reaction to β-lactam antibacterials than patient history alone, but this method still over-estimates the rate of IgE-mediated events in 66% of patients.[34] Because of these statistics, recent studies have looked at ways of testing for allergic reactions before offending agents are prescribed. Some of these studies will be discussed in section 3.2.1.

There are a number of factors which appear to affect the incidence and severity of anaphylaxis and anaphylactoid reactions that must be considered when evaluating patients. Women seem to have more frequent anaphylactic reactions to intravenous muscle relaxants containing quaternary ammonium ions than men.[35] This may be a result of prior sensitisation through exposure to these ions via cosmetics. The route of administration of the offending agent increases both the frequency of occurrence and the severity. Events may occur if given by any route, but are most frequent and severe with the intravenous route.[5] If prior therapy was interrupted, creating gaps in administration, there is an increased risk of subsequent reaction.[36] Finally, studies have shown that the greater the number of years since the last administration of the offending agent, the less chance of recurrence of reactions.[5]

Depending on the history of the reaction offered by the patient, a number of paths may be taken. The first is to simply substitute the offending agent with another that is not cross-reactive but offers a similar effect. When that is not possible, and the clinician has a high level of suspicion that the prior reaction was allergic in nature, skin testing may be performed. This is outlined in section 3.2.2. Results can then be used, weighted by the patient's history of reaction, to decide if the medication could be administered using a desensitisation protocol. There are certain instances when a medication should never be re-administered. These include life-threatening reactions such as exfoliative dermatitis syndromes and dermatoses with mucous membrane lesions (Stevens-Johnson syndrome-like).[37]

Clinicians need to weigh up the health of the individual with the benefits and risks of administration of the agent in question. There are situations which demand certain medications, such as neurosyphilis.[38] Patients with this disease require intravenous penicillin even if they have a positive history and skin test to penicillin, so desensitisation is crucial. At other times, serious underlying medical problems, such as severe coronary heart disease or multisystem organ failure, may make desensitisation an unattractive option.

An example of a specific physical finding which affects the risk of anaphylactoid reactions is nasal polyps in patients with asthma. As discussed previously, the incidence of anaphylactic reaction in these patients when given aspirin or NSAIDs is as high as 97% in some studies.[16]

3.2 Other Preventative Strategies

There are other simple measures that can be implemented to reduce the incidence of anaphylaxis and related mortality. As mentioned above, parenteral administration of drugs increases the frequency and severity of reaction. When drugs are given intravenously, the patient should remain under medical supervision until 20 to 30 minutes after

administration. Patients with a documented history of anaphylaxis should wear a Medic-Alert bracelet or necklace and keep an identification card in their purse or wallet to alert medical personnel in case of emergency. Patients should also have on their person an epinephrine (adrenaline) kit for self administration in case of problems.

Certain medications should be avoided in patients with a history of anaphylaxis. These include β-adrenoceptor antagonists, ACE inhibitors, angiotensin II receptor antagonists, monoamine oxidase inhibitors and tricyclic antidepressants. β-Adrenoceptor antagonists decrease epinephrine's effectiveness. ACE inhibitors and angiotensin II receptor antagonists reduce the body's ability to activate compensatory mechanisms in the face of a hypotensive crisis. The monoamine oxidase inhibitors and certain tricyclic antidepressants enhance the adverse effects of epinephrine administration such as tachycardia and hypertension.[5]

3.2.1 Diagnostic Testing for Drug Hypersensitivity

There are 3 methods of testing for drug sensitivity. *In vivo* skin testing for immediate reaction to the suspected agent is one mode. The second involves *in vitro* determination of drug-specific IgE from the affected patient's blood. A major problem with diagnostic testing is that in most cases, except for penicillin, the principal drug allergen is unknown. The third type of testing is an oral challenge.

3.2.2 Skin Testing

Prick and intradermal testing are performed to assess immediate IgE allergic reaction. Prick testing uses a small amount of test solution containing the suspect medication which is placed on the skin. A sterile needle or standard SPT lancet is then placed through the test solution into the epidermis and gently lifted upward. The area is evaluated after 15 minutes for a wheal or flare reaction that is greater than seen with the positive control histamine. Intradermal injection of potential allergen can be used if the prick test is negative. Intradermal skin tests increase the sensitivity of the testing. Three case reports in the literature have related death to skin testing by prick or intradermal methods for penicillin allergy.[39] Skin testing may not be indicated in patients with a convincing history by which the medication in question caused a severe reaction.[39] Prick and skin testing can be performed to test for β-lactam antibacterials, latex and local anaesthetics.

The mechanism of immune system activation for penicillin is well documented. During degradation, a number of metabolites are formed. The major antigenic determinant is the penicilloyl moiety. Most penicillin-reactive patients create antibodies to this component. Other antigen were discovered that cause reactions, but in fewer patients, the minor antigenic determinants. *In vivo* skin testing utilises penicilloyl polylysine to test for the major determinant and benzylpenicillin (penicillin G) for the minor determinant. Testing for both the major and minor determinants is necessary in the assessment of penicillin allergy.[41]

Taking the history along with the skin test results, a clinician can interpret future risk of reaction upon retreatment with the agent. Unfortunately, the rate of false negative tests is only known for some antibacterial agents.[40] One large outpatient study was conducted in 1993 at an inner city sexually transmitted disease clinic and from this, data predictions for penicillin can be made. Allergic reactions observed in patients with a positive history and a negative skin test at the time of readministration of penicillin were virtually all mild and self limited. There were no life-threatening reactions reported.[42]

Some other drugs including other β-lactam antibacterials, ciprofloxacin, trimethoprim, cisplatin, neuromuscular blocking agents, thiobarbiturates, some anticonvulsants and local anaesthetics elicit a positive skin test in their native form. Standardised skin testing for medications, however, has only been established for penicillin. It should be noted that the intravenous preparation of ciprofloxacin is highly irritative to skin so if used for skin testing must be diluted. Insulin and other native or recombinant proteins are complete antigens and thus can be used to yield reliable skin tests when used in appropriate concentrations.[40]

Eggleston and Lush[24] recommended skin testing for local anaesthetics in patients with a history of allergy or drug exposure that was unclear. They noted that if prick testing was not definitive then intradermal skin testing should be performed. However, a positive reaction to intradermal tests in patients with a history of allergic reaction occurred only 25% of the time. In history-negative controls, a positive reaction occurred 9% of the time. Therefore skin testing is not definitive in assessing anaesthetic allergy. Patch testing using topical local anaesthetic agents was discussed as a way of assessing delayed-type hypersensitivity, but was not found to be very helpful.

Li et al.,[43] in an attempt to decrease the amount of vancomycin given prophylactically for orthopaedic procedures in patients with a history of penicillin allergy, used skin tests to the major and minor determinants of penicillin to determine true IgE-mediated reaction. 60 patients were enrolled in the study. 48 of the 60 gave a history of allergy to penicillin, 2 gave a history of cephalosporin allergy, 5 gave history of both penicillin and cephalosporin allergy and 5 gave an unclear history of an allergic reaction to an antibacterial. 59 patients had skin tests performed. 55 (93%) had a negative skin test and 4 had 1 or more positive skin tests. There were no distinguishing features in the medical history of the patients with positive skin tests. 55 of the patients had prophylactic antibacterials at surgery. 49 (89%) were given cefazolin and 6 (11%) were given vancomycin. None of the 55 patients given prophylactic antibacterials had an immediate reaction. One patient did develop a rash several days later, but that patient had been taking many medications at the time.

3.2.3 Other Diagnostic Testing

The radioallergosorbent test (RAST) and other immunoassays testing for drug-specific IgE antibodies in serum are not very sensitive. Currently, a commercial RAST assay is produced for the major determinant of penicillin, but not for the minor determinants. Those patients without IgE to the penicilloyl determinant but with antibodies to one of the minor determinants will be missed. RAST assays are available for insulin, latex and neuromuscular blockers, but negative tests must be interpreted with caution. For many other medications the antigenic component is unknown. It is therefore difficult to evaluate a negative test.[40]

Oral challenges can be performed under supervision. In recent studies, these challenges have been used in conjunction with skin testing to identify the negative predictive value of skin tests as well as to assess possible cross-reactivity reactions.[34] In children and adults, oral challenges are done using a standard dose in either tablet, capsule of liquid form. The individual is then monitored for 30 minutes to detect any immediate reactions.

Macy[4] used elective skin testing prior to acute administration of antibacterials, and amoxicillin challenge in those with negative skin tests. 236 patients underwent penicillin skin test using penicillin, benzylpenicilloyl polylysine, amoxicillin, penilloate and penicilloate. 196 (83%) patients were skin test negative, and, of those, 146 agreed to amoxicillin challenge. Eight (5.5%) of the amoxicillin challenge patients reported an adverse reaction, and 4 of those tolerated a penicillin antibacterial later in the study period. There were 15 patients with positive penicillin skin tests who received at least 1 course of cephalosporin therapy. There were no immediate reactions, and only 1 delayed reaction that was believed to be serum sickness. The study also demonstrated that the resensitisation rate in adults with a negative penicillin skin test after therapeutic penicillin antibacterial administration was 3.2%, substantially less than previous estimates of 20%.[44]

In the paediatric population, Pichichero and Pichichero[34] also used elective skin testing in patients with a history of β-lactam allergy. 247 children and adolescents were enrolled. Skin testing to benzylpenicillin, benzylpenicilloyl phosphate, penicillin minor determinant mixture, ampicillin, cefazolin and ceftriaxone was completed. If the intradermal skin test was negative the patient was given a penicillin oral challenge and observed for 30 minutes for immediate reaction. If there was no immediate reaction then a 5 to 10 day challenge of

the β-lactam antibacterial that caused the historical adverse reaction was administered. 53 (21.5%) of the 247 skin tested children had an initial positive reaction. 194 were skin test negative and were given a 10-day course of antibacterial. After the challenge, the children had skin tests repeated. 26 (10.5%) of the 247 were positive to skin test during the second test period. 163 (66%) were both skin test negative and challenge negative and were allowed to reinitiate therapy with β-lactam antibacterials. The rest were advised to avoid the tested β-lactams. Multiple courses of penicillins and cephalosporins were administered to the skin test-negative group during the 6-month to 8-year follow-up. Only 3 (1.8%) children experienced an adverse IgE-mediated reaction, and all were mild. 84 children with a positive skin test or oral challenge to penicillins were advised that they could receive cephalosporins. Two children (2%) developed a mild IgE-type reaction, and both had a positive reaction to prick or intradermal skin testing to more than one penicillin reagent.[34]

4. Management

In the midst of the acute anaphylactic or anaphylactoid event, immediate action is lifesaving. The initial steps in the management of anaphylaxis are the same as for all life-threatening events which are the control of airway, breathing and circulation. One must assess the patient's airway, and if compromised this must be rectified immediately. Blood pressure and pulse should be checked. The patient should be placed in a supine position with feet elevated. Modifications must be made in positioning if the patient is wheezing. Oxygen should be started and the patient's bodyweight should be estimated for medication dosage determinations.

Epinephrine should be administered during the above mentioned procedures. The route depends on what is most immediately available. In either children or adults in an office setting, intramuscular or subcutaneous administration can be utilised. The intramuscular dose for adults, using 1 : 1000 epinephrine, is 0.3 to 0.5ml (0.3 to 0.5mg). In children the dose is 0.01 mg/kg. The dose can be repeated as necessary at 10 to 15 minute intervals 2 to 3 times.[5] The intramuscular route was found to be the route of choice in a study done by Simons et al.[45] which evaluated the absorption of epinephrine given by either subcutaneous or intramuscular injection.

If the patient is found to be severely hypotensive then intravenous access must be obtained. Epinephrine as well as intravenous fluids need to be initiated. A suggested protocol is as follows: 0.1ml (0.1mg) of 1 : 1000 aqueous epinephrine solution can be diluted in 10ml of normal saline. The 10ml dose can then be infused over 5 to 10 minutes resulting in a total dose of 100μg at a rate of 20μg per minute. Repeating the dose would be dependent on response, with dose escalation reflecting more critical situations. If a constant infusion is required, the patient needs to be monitored for cardiovascular complications. There is a commercially available 1 : 10 000 epinephrine formulation that is available in a 10ml syringe. If intravenous access is not obtainable, sublingual injection may be tried since it is richly vascular. The intramuscular dose can be injected into the posterior one-third of the sublingual area. If the patient is intubated, epinephrine can be given via the endotracheal tube. The dose in children is 0.1 mg/kg or 0.1 ml/kg for a 1 : 1000 solution. The dose in adults is unknown. Recommendations[5] are to start at 1mg, but up to 2 to 2.5 times the intravenous dose may be necessary. The dose will be rapidly absorbed after 5 to 10 breaths.

Intravenous fluids help restore intravascular volume lost with fluid shifting from the intravascular to the extravascular space during anaphylaxis. Large volumes may be required and fluid must be infused rapidly. 1000 to 2000ml of crystalloid solution, either normal saline or lactated Ringer's, should be given rapidly depending upon the patient's blood pressure. A rate of 5 to 10 ml/kg can be infused over the first 5 to 10 minutes. Children should receive a 30 ml/kg bolus of crystalloid solution in the first hour. If colloid solution is preferred, adults should receive 500ml followed by a slow infusion thereafter. If large amounts of fluids

are required, these patients will require intensive monitoring to help guide volume status. This may include monitoring of central venous pressure, pulmonary artery wedge pressure, cardiac output, oxygen consumption, urinary output and electrocardiographic monitoring.

In certain situations of recalcitrant hypotension, vasopressors may be used. Their effectiveness is limited if the patient's peripheral vascular resistance is already elevated from endogenous compensatory mechanisms. Vasopressors have been used for years and can be helpful. Dopamine is the drug of choice in most instances. A rate of 2 to 20 μg/kg/minute should be adjusted according to effect on the patient's blood pressure.

An important caveat is the patient treated with a β-adrenoceptor antagonist for baseline hypertension. This patient can experience recalcitrant hypotension, at times requiring up to 5 to 7 litres of fluid. In such patients glucagon, a glycopeptide produced by the α-cells of the pancreas, produces both inotropic and chronotropic effects. The dose is 1 to 5mg intravenously as determined by clinical response. This dose may need to be followed by a continuous infusion of 5 to 15μg per minute titrated again to clinical response. Cardiotonic effects of glucagon are seen in 1 to 5 minutes and are maximal at 15 minutes. Administration may be limited by nausea and vomiting. In the case of isolated bradycardia, atropine given at a dose of 0.3 to 0.5mg either intramuscularly or subcutaneously every 10 minutes, to a maximum dose of 2mg, may be beneficial. If the patient receiving a β-adrenoceptor antagonist has bronchospasm but not shock, aminophylline becomes the drug of choice. It should be used very cautiously if hypotension is present.

Histamine receptor antagonist therapy can be used with epinephrine, although it is not considered to be lifesaving. It may offer dramatic relief of symptoms in selected patients. Clinical trials have shown that combinations of histamine H_1 and H_2 receptor antagonists are superior to H_1 receptor antagonist monotherapy.[46] In adults, diphenhydramine may be given by the intramuscular or intravenous route, depending on the severity of the situation, at a dose of 25 to 50mg. Children can be administered the medication by the oral, intramuscular or intravenous route at a dose of 1 to 2 mg/kg. Ranitidine can be given at a dose of 1 mg/kg.

The role of corticosteroids in the management of acute events is unclear. The use of these agents makes good sense, based on findings in other allergic diseases. Their use is especially salient because of their theoretical effects on the late phase reaction. Anaphylaxis can be biphasic, and prevention of the second phase may be crucial. Studies are still somewhat lacking in this area of treatment, and there is no established drug of choice. Patients with milder anaphylactic reactions may benefit from 30 to 60mg of oral prednisone. Methylprednisolone can be used if an intravenous agent is required. The usual dose can range from 125 to 250mg depending on the clinical situation.

If wheezing occurs that is unresponsive to epinephrine, aerosolised β-adrenoceptor antagonists, and if necessary aminophylline, may be used. The doses are the same as for asthma. β-Agonists 0.25 to 0.5ml are administered in 1.5 to 2.0ml of saline every 4 hours unless required more frequently. Aminophylline is administered intravenously in adults and children over the age of 1 year, starting with a loading dose of 6 mg/kg given over 20 to 30 minutes.

Patients need to be observed after stabilisation for at least 2 hours for mild episodes and probably for 24 hours after severe anaphylaxis. There is the possibility of a biphasic episode and if this is not recognised and treated results can be deadly.[5]

5. Conclusion

Anaphylaxis and anaphylactoid reactions are potentially life-threatening events. Many different agents can cause them. Prevention, if possible, is the purpose of detailed patient history taking and physical examination. Testing is available, but the exact antigenic determinant of many medications is unknown, making a negative test difficult to interpret. Desensitisation procedures, as well as gradual dose escalation protocols, are available and are implemented based on history and diagnostic test-

ing. The treatment of anaphylaxis is based on control of the airway, breathing and circulation. Treatment revolves around epinephrine and supportive measures. All individuals with a documented history of anaphylaxis require a Medic-Alert bracelet or necklace, and an identification card for their wallet of purse.

References

1. Kagy L, Blaiss MS. Anaphylaxis in children. Pediatr Ann 1998 Nov; 27 (11): 727-34
2. Freeman TM. Anaphylaxis: Diagnosis and Treatment. Primary Care; Clinics in Office Practice 1998 Dec; 25 (4): 809-17
3. Hess DA, Rieder MJ. The Role of Reactive Drug Metabolites in Immune-Mediated Adverse Drug Reactions. Ann Pharmacother 1997 Nov; 31 (11): 1378-87
4. Macy E. Elective penicillin skin testing and amoxicillin challenge: Effect on outpatient antibiotic use, cost and clinical outcomes. J Allergy Clin Immunol 1998 Aug; 102 (8): 281-5
5. Lieberman, P. Anaphylaxis and Anaphylactiod Reactions. In: Middleton E, Reed CE, Ellis EF, et al., editors. Allergy principles and practice. St. Louis: Mosby, 1998: 1079-91
6. Douglas DM, Sukenick E, Andrade WP et al. Biphasic systemic anaphylaxis: An inpatient and outpatient study. J Allergy Clin Immunol 1994 Jun 93 (6): 977-85
7. Atkinson TP, Kaliner MA. Anaphylaxis. Med Clin Nor Am 1992; 76: 841-55
8. Boston Collaborative Drug Surveillance Program: Brief reports: drug induced anaphylaxis, JAMA 1973; 224: 613
9. Porter J, Jick H. Boston Collaborative Drug Surveillance Programs: drug induced anaphylaxis, convulsions, deafness and extrapyramidal symptoms. Lancet 1977; I: 587
10. Amornmarn L, Bernard L, Kumar N, et al. Anaphylaxis admissions to a university hospital. J allergy Clin Immunol 1992; 89 Suppl.: 349
11. Bresser H, Sander C, Rakoski J. Anaphylactic emergencies in Munich. J Allergy Clin Immunol 1995; 95: 386
12. Klein JS, Yocum MN. Underreporting of anaphylaxis in a community emergency room. J Allergy Clin Immunol 1995; 95: 637-8
13. Yocum MW, Butterfield JH, Klein JS, et al. Epidemiology of anaphylaxis in Olmstead County: a population-based study. J Allergy Clin Immunol 1999: 104: 452-6
14. Weiss ME, Atkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy 1988: 18: 515-40
15. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States. Arch Intern Med 2001; 161: 15-21
16. Falliers, CJ. Aspirin and subtypes of asthma: risk factor analysis. J Allergy Clin Immunol 1973; 52: 141
17. Manning ME, Stevenson DD, Mathison DA. Reactions to aspirin and other nonsteroidal anti-inflammatory drugs. Immunol Allergy Clin North Am 1992 Mar; 12 (3): 611-31
18. Strom BL, Carson JUL, Morse ML, et al. The effect of indication on hypersensitivity reactions associated with zomepirac sodium and other non-steroidal anti-inflammaotry drugs. Arthritis Rheum 1987; 30: 1142
19. Settipane GA, Chafee FH, Klein DE. Aspirin intolerance: II. A prospective study in an atopic and normal population. J Allergy Clin Immunol 1974; 53: 200
20. Kemp SF, Lockey RF, Lieberman P, et al. Anaphylaxis, a review of 266 cases. Arch Intern Med 1995; 155: 1749-54
21. Laxenaire MC, Moneret-Vautrin DA, Widmer S, et al. Substances anesthesiques responsables de chocs anaphylactiques. Enquete multicentrique francaise. Ann Fr Anesth Reanim 1990; 9: 501-6
22. Laxenaire MC, Le Groupe d'etude des reactions anaphylactoides peranesthesiques. Substances responsables des chocs anaphylactiques peranesthesiques: troisieme enquete multicentrique francaise (1992-1994). Ann Fr Anesth Reanim 1996; 15: 1211-8
23. Gueant JL, Aimone-Gastin I, Namour F, et al. Diagnosis and pathogenesis of the anaphylactic and anaphylactoid reactions to anaesthetics. Clin Exp Allergy 1998; 28: 65-70
24. Eggleston ST, Lush LW. Understanding allergic reactions to local anesthetics. Ann Pharmacother 1996; 30: 851-7
25. Giovannitti JA, Bennett CK. Assessment of allergy to local anesthesia. J Am Dent Assoc 1979; 98 (5): 701-6
26. Lagier F, Vervloet D, Lhermet, I et al. Prevalance of latex allergy in operating room nurses. J Allergy Clin Immunol 1993; 90: 319-22
27. Kelly KJ, Walsh-Kelly CM. Latex allergy: A patient and health care system emergency. J Emerg Nurs 1998 Dec; 24 (6): 539-45
28. Latex Hypersensitivity Committee of the American College of Allergy, Asthma, and Immunology: Latex allergy an emerging health care problem. Ann Allergy Asthma Immunol 1995; 75: 19-21
29. KatayamaH, Yamaguchi K, Kozuka T, et al. Adverse reactions to ionic and nonionic contrast media: a report from the Japanese Committee on the Safety of Contrast Media. Radiology 1990; 175: 621
30. Adkinson FN. Drug allergy. In: Middleton E, Reed C, Ellis EF, et al., editors. Allergy principlesand practice. St Louis: Mosby, 1998: 1217
31. Adkinson NF. Beta-lactam crossreactivity. Clin Exp Allergy 1998; 28 (4) 37-40
32. Craig TJ, Mende C. Common allergic and allergic-like reactions to medications. Postgrad Med 1999 Mar; 105 (3): 173-81
33. Sogn DD, Evans III R, Shepard GM, et al. Results of the National Institutes of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derviatives in hospitalized adults. Arch Intern Med 1992; 152: 1025-32
34. Pichichero ME, Pichichero DM. Diagnosis of penicillin, amoxicillin and cephalosporin allergy: reliability of examination assessed by skin testing and oral challenge. J Pediatr 1998 Jan; 132: 137-43
35. Vervloet D, Arnaud A, Vellieux P, et al. Anaphylactic reactions to muscle relaxants under general anesthesia. J Allergy Clin Immunol 1979; 63: 348
36. Lieberman P. Difficult allergic drug reactions. Immunol Allergy Clin North Am 1991; 11 (1): 331
37. Wolkenstein P, Revuz J. Drug-induced severe skin reactions. Drug Safety 1995; 13 (1): 56-68
38. Gleckman RA, Borrego F. Adverse reactions to antibiotics. Postgrad Med 1997 Apr; 101 (4) 97-108
39. Valyasevi MA, Van Dellen RG. Frequency of systematic reactions to penicillin skin tests. Ann Allergy Asthma Immunol 2000 Nov; 85 (5): 363-5
40. Gruchalla R. Understanding drug allergies. J Allergy Clin Immunol 2000; 105: 637-44

41. Solley GO, Gleich GJ, Van Dellen RG. Penicillin allergy: clinical experience with a battery of skin-test reagents. J Allergy Clin Immunol 1982; 69: 238-44
42. Gadde J, Spence M, Wheeler B, Adkinson NF. Clinical experience with penicillin skin testing in a large inner city STD clinic. JAMA 1993; 270: 2456-63
43. Li JTC, Markus PJ, Osmon DR, et al. Reduction of vancomycin use in orthopedic patients with a history of antibiotic allergy. Mayo Clin Proc 2000; 75: 902-6
44. Parker DJ, Parrinello JT, Condemi JJ, et al. Penicillin resensitization among hospitalized patients. J Allergy Clin Immunol 1991; 88: 213-7
45. Simons PR, Roberts JR, Gu X, et al. Epinephrine absorption in children with history of anaphylaxis. J Allergy Clin Immunol 1998; 101: 33-7
46. Mayumi H, Kimura S, Asano M, et al. Intravenous cimetidine as an effective treatment for systemic anaphylaxis and acute allergic skin reaction. Ann Allergy 1987; 58: 447-50

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