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Prescription Of Epinephrine Auto-Injectors – Can We Reach A Consensus?

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Abstract
Anaphylaxis is a potentially life-threatening allergic reaction, in which prompt administration of epinephrine may be life-saving. Epinephrine is available as an autoinjector for self-administration, or administration by parents and other non-medical personnel. There is considerable debate about who should be prescribed such autoinjectors. The Immunology Group of Ireland represents consultant immunologists, immunology nurse specialists, clinical scientists and trainees in immunology. In the absence of a firm evidence base on which to make such decisions, this consensus statement summarises the opinion of the group. Epinephrine autoinjectors should be prescribed to patients who are at definite risk of a further life-threatening reaction (those previously requiring adrenaline during resuscitation where further exposure to the allergen cannot be excluded; those with generalised allergic reactions and additional risk factors such as asthma, limited access to care, reactions to trace amounts of allergen, or allergens causing a high incidence of hypotensive reactions; severe venom allergy and patients with idiopathic anaphylaxis). Autoinjectors may be recommended in patients allergic to anaphylaxis-prone allergens such as nuts or shellfish and patients who have had generalised allergic reactions and have other co-morbidities which increase the risk associated with an episode of anaphylaxis.

Prescription of epinephrine is not recommended for asthma in the absence of systemic reactions to allergen, positive allergy tests in the absence of clinical reactivity, family rather than personal history of anaphylaxis, and drug allergy even when severe reactions have occurred. When prescribing epinephrine, responsibility should be taken for patient education about allergen avoidance as well as when and how to use the epinephrine; review of medical co-morbidities and concomitant medication; optimisation of asthma control; provision of a detailed emergency plan and arranging appropriate follow-up. Options such as public availability of epinephrine, as well as increased numbers of ambulance personnel and first responders trained to administer epinephrine may enhance the safety of people with potentially life-threatening allergies, and should be assessed. There is a need for large follow-up studies of patients who carry autoinjectors to provide evidence on which to base more rational prescribing in the future.

Introduction

The incidence of all forms of allergic diseases is rising sharply. Allergy to food, venom and drugs is also becoming more common, and these allergens frequently cause generalised reactions, including anaphylaxis. Anaphylaxis is potentially life threatening, frequently involves multiple systems and characteristically includes the occurrence of hypotension, severe bronchospasm or laryngeal oedema usually, but not always associated with cutaneous or other allergic phenomena.[1] Good epidemiological data on the frequency with which anaphylactic reactions occur is lacking and comparison of existing studies is hampered by the lack of a standardised definition. Hence the true incidence of anaphylaxis is uncertain. The Rochester Epidemiology Project, a retrospective population-based study in Olmsted County, Minnesota demonstrated an incidence of anaphylaxis of 21 per 100,000 person- years, with an anaphylaxis occurrence rate of 30 per 100,000 person-year.[2] However, this study was based on data collected in the mid-80s and so is likely to underestimate the current incidence of anaphylaxis. The proportion of the US population calculated to be at risk from anaphylaxis due to food, drugs, latex or stings is between 1.2 and 15%.[3] Anaphylaxis has been shown to be responsible for 1 in 1100 emergency room attendances in the US,[4] with figures of between 1 in 1500 and 1 in 2300 demonstrated in a retrospective study in a UK accident and emergency department.[5] While the recognised mortality due to anaphylaxis is less than 1 per 2.5 million of the population per year, this is likely to be an underestimate, as asthma due to food allergy may not be recognised as such, and recorded as an asthma death.[6] Amongst fatalities recognised to be due to anaphylaxis, approximately half are due to drug allergy, with the remainder split between food and venom allergy.[6] Mortality in children appears lower than the general population, with a study of children under 16 in the UK and Ireland (paediatric population approximately 13 million) identifying only 8 deaths over a 10 year period attributed to recognised food allergy.[7]

Allergic sensitisation is confirmed by the demonstration of allergen specific IgE in vivo or in vitro, or in selected cases by the use of provocation testing. However, no testing methods or set of risk factors reliably identify those at risk of anaphylaxis rather than a non-life-threatening allergic response.[8, 9, 10, 11] While anaphylaxis can be caused by virtually any ingested or injected allergen, some allergens have been reported to cause a relatively high proportion of anaphylactic reactions. Such anaphylaxis prone allergens include nuts, fish and shellfish, venom and medications, particularly beta-lactams. However, severe or fatal reactions are seen in response to many allergens including allergies generally perceived to be "benign" such as milk.[7,8,9] Patients with asthma in addition to an allergy to anaphylaxis causing allergens may suffer severe bronchospasm as a component of the allergic reaction[3] and poorly controlled asthma is an important risk factor for fatal or near fatal anaphylaxis.[6,7] A history of food allergy has been strongly associated with severe paediatric asthma that requires management in an intensive care setting.[12] Patients who have experienced severe reactions are thought to be at increased risk of subsequent severe reactions. Unfortunately, the converse is not true, and patients with mild reactions may subsequently experience severe or even fatal reactions.[6,13]

The number of people allergic to allergens prone to cause anaphylaxis is an important factor determining the number of people at potential risk of anaphylaxis. The food allergy most commonly associated with severe allergic reactions is peanut and tree nut allergy. The incidence of peanut allergy has now exceeded 1% of children in several parts of the developed world.[14,15] While many peanut allergic individuals will not develop anaphylaxis, the absence of clear predictive factors does not allow reassurance of those patients at low risk. A diagnosis of potentially dangerous allergy is associated with significant anxiety and greatly impaired quality of life. A study of children aged 7 to 12 years showed greater impairment of disease related quality of life in children with peanut allergy than in children with insulin dependent diabetes mellitus.[16] Although less well studied, it is likely that allergy to other allergens prone to cause anaphylaxis and difficult to avoid (such as fish, latex and venom) would have similar psychological sequelae.

Administration of epinephrine is recommended for the treatment of anaphylaxis by medical first responders, and the effectiveness of this drug is widely recognised, although not established in

randomised controlled trials.[17] Epinephrine for self-administration is frequently prescribed to patients perceived to be at risk of severe reactions for use in emergencies. However, the evidence on which such estimates of risk are based, as well as evidence for the effectiveness of this form of treatment is limited. From an ethical point of view, randomised controlled trials to assess the effectiveness of self-administered epinephrine could not be performed and therefore difficult, empirical decisions are required in practice.[18] The frequency with which epinephrine autoinjectors are prescribed has provoked debate, with some authors suggesting that they are vastly over-prescribed[19], while other experts recommend making self-administered epinephrine widely available to patients with food allergy[20], particularly peanut allergy.[21,22]

In the absence of a sound evidence base, the decision to prescribe epinephrine for self-administration is based on the perceived benefit versus the perceived risks of such treatment. Administration of epinephrine is highly effective in most, but unfortunately not all, severe allergic reactions. A pilot programme assessing administration by ambulance personnel showed that treatment was effective in 77% of the 37 patients treated, with 20% unchanged, while 3% continued to deteriorate.[23] Gold & Sainsbury followed up 121 patients who had been prescribed an autoinjector, 45 of whom had potentially life-threatening reactions. Of the 13 patients who used their autoinjector appropriately, only 2 subsequently required additional treatment in the emergency room, while 15 of the 32 who did not use the autoinjector required epinephrine in the emergency room, and had a higher rate of admission.[24] Perhaps most persuasive is the frequency with which lack of availability of epinephrine is described in fatal cases, both in the UK register[6] and the US, where only 10% of cases identified had an epinephrine autoinjector available at the time of their fatal reaction.[25]

The safety of epinephrine has been debated. However, the majority of adverse events described have been related to intravenous administration of epinephrine, or administration of excessive doses.[6,7,26,27,28] However, there is general consensus that intramuscular administration of 1:1000 dilution of epinephrine in doses of 0.01mg/kg to a maximum of 0.4 mg is safe.[28,29] Patients with underlying ischaemic heart disease require careful monitoring and avoidance of overdose is important, however, the risks of untreated anaphylaxis with a decreased cardiac filling pressure exceed the risk of adrenaline administered in appropriate dosage.[30] In addition to the medical side effects of epinephrine, there is a need for further research to establish the psychosocial effects of autoinjector prescription. While many patients welcome the availability of a further safety net for themselves or their child, in some patients the prescription of an autoinjector appears to heighten anxiety.[18,31] It remains to be established if the expertise of the prescribing physician affects the level of anxiety or reassurance induced in this situation.

Prescription of epinephrine for self-administration and patient education does not guarantee the appropriate administration of epinephrine, with rates of administration during severe reactions as low as 29%.[22] While clearly work is needed on how best to improve education and confidence in patients, parents and other caregivers, it is worth bearing in mind that only 5% of senior house officers at the start of accident and emergency posts were able to indicate the correct dose and route of adrenaline according to UK Resuscitation Council Guidelines.[32]

While epinephrine autoinjectors are safe and usually effective, it is important to ensure that adequate emphasis is placed on allergen identification and education about allergen avoidance.[33] Fatalities have been reported even when several autoinjectors were correctly used.[8] The success of an integrated management plan for nut allergy has been described by Ewan and Clark, with verbal and written information about allergen avoidance given to patients, parents and school staff, as well as training in recognition and treatment of reactions with a written treatment plan, together with follow-up and retraining. Autoinjectors were prescribed for patients felt to be at risk of severe reactions (previous severe reactions, reaction to trace amounts, concomitant asthma). Following this management plan, there was a relatively low incidence of further reactions (15%), with only one of 172 patients who had not been given an auto-injector requiring administration of epinephrine in A & E. All other patients successfully self treated.[34,35]

Epinephrine for self-administration can be prescribed as vials of epinephrine to be drawn up by the patient, pre-filled syringes (1mg in 1ml) or as preloaded auto-injector devices, which administer a dose of 300µg (or 150µg in the paediatric versions). These auto-injectors offer the advantages of ease of use, are more acceptable to patients, as well as avoiding overdosing due to errors drawing up the solution from a vial. Disadvantages include the risk of misfiring and failure to deliver the full dose as well as the limited length of the needle, which may not ensure intramuscular administration in obese patients.[36] Two proprietary epinephrine auto-injectors are available – the AnaPen and the EpiPen. Use of the EpiPen involves removing the device from the container, removing the safety cap and pressing the needle-containing end against the thigh for 10 seconds. Use of the AnaPen involves removal of the needle cap, removal of the safety cap, placing the pen against the thigh and pressing the button for 10 seconds. Only the AnaPen is currently licensed in the Republic of Ireland.

Process

The Immunology Group of Ireland (IgI) is a group of clinical immunologists from both the Republic of Ireland and Northern Ireland. Current practice and uncertainties in relation to prescription for epinephrine for self-administration were debated and the outcome of discussions summarised, circulated and discussed at 2 further meetings of the group. The final draft was reviewed by all members of the group. The following statement summarises the consensus reached.

Consensus on the prescription and use of self-administered epinephrine

This document summarises recommendations agreed by the Immunology Group of Ireland concerning the prescription of self-administered epinephrine and related issues.

Allergen avoidance is the mainstay of allergy management. Every effort should be made to identify the allergens responsible for patients' reactions. Thorough patient education about allergen avoidance, asthma management and the patient's individualised emergency plan, which may require written advice and repetition, is required. Epinephrine for self-administration is only part of a comprehensive emergency plan, including detailed information on management of uneventful accidental exposures, minor reactions as well as severe reactions for which epinephrine administration is indicated. However, provision of an epinephrine for self-administration should not replace or detract from allergen identification and patient education.

Factors to consider when evaluating the need for self-administered epinephrine

Every effort should be made to obtain a specialist opinion prior to prescribing epinephrine. If it is considered essential to prescribe epinephrine prior to full assessment and diagnosis, the patient should be advised that this is an interim measure and that a decision about the long-term requirement for such measures will be taken by the specialist after full assessment. As with prescribing any medication, the decision to prescribe epinephrine for self-administration should only be made when the anticipated risks are outweighed by the perceived benefits. Factors impacting on the risk : benefit ratio include:

History of clinical reaction severity and frequency

More severe reactions and also more frequent reactions particularly if the allergen responsible cannot be delineated in all cases would favour prescription of epinephrine for self-administration. However, a history of mild reactions does not exclude future severe reactions.

Allergen involved and the ability of the patient to avoid it

Some allergens such as medications can be successfully avoided with appropriate education and provision of emergency medications should not be needed. However, allergy to common foodstuffs makes allergen avoidance difficult and even the most conscientious patients can be expected to have accidental exposures.

Age of patient

Fatal anaphylactic reactions are extremely rare in children under the age of 5. While this in part may be due to the ability of parents to successfully control the diet of this age group, this epidemiological observation impacts on the risk : benefit ratio of epinephrine for self-administration in this age group. The decision not to provide autoinjectors for any individual infant needs regular review because asthma may develop after the food allergy has been identified (increasing risk), new food allergies may be identified (increasing risk), the child may enter day care or school (possibly increasing risk) or the food allergies or existing asthma may resolve (decreasing risk). Similar reasons exist for reviewing existing prescriptions for autoinjectors as removal of autoinjectors that are no longer required may reduce anxiety; facilitate involvement in a full range of social activities as well as increasing options for day care etc.

Other co-morbidities

The presence of asthma, particularly if poorly controlled at the time of allergen exposure, is a major factor contributing to poor outcomes. The presence of ischaemic heart disease is not a contraindication to the appropriate use of epinephrine as patients are at increased risk due to poor cardiac filling pressures during anaphylaxis. However, inappropriate use of epinephrine carries increased risks of precipitating further ischaemia.

Concomitant medications

Medications such as beta-blockers, ACE inhibitors and NSAIDs can increase the severity of an allergic reaction. Additionally, medications such as tricyclic antidepressants, monoamine reuptake inhibitors and alpha- and beta-adrenergic blockers interact with epinephrine, making the use of epinephrine more hazardous. Cocaine, hyperthyroidism and exposure to chemicals used in refrigeration sensitise the heart to the arrhythogenic effects of epinephrine. It is essential that all medications are reviewed and appropriate substitutions made when epinephrine for self-administration is prescribed. In the case of beta-blockers prescribed for heart disease, careful consideration of the risks and benefits should be undertaken in collaboration with the patient's cardiologist, as in many cases discontinuing the beta blocker may be associated with a greater risk of mortality.[37]

Psychological and practical implications of carrying the device

For some patients and their families possession of epinephrine for self-administration reduces anxiety, while for others possession of epinephrine is an additional source of stress.

Willingness and ability of the patient to carry their emergency pack

Clearly epinephrine is only of value when the patient has it to hand when an emergency arises. If there is a strong indication to carry epinephrine, every effort must be made to ensure that the patient is fully informed of the issues. However, when the indication is less clear-cut, patient input into the decision following discussion of the advantages and disadvantages of carrying epinephrine is important. This discussion should be clearly documented in medical notes.

Lifestyle and geographical factors affecting access to emergency medical care

Patients who live in remote areas, or whose occupations or hobbies increase their risk of allergen exposure or bring them to remote areas need to be more self-sufficient. Therefore, it may be appropriate to lower the threshold to prescribe epinephrine. Geographical factors are also likely to impact significantly on the number of devices prescribed.

Prescription of epinephrine for self-administration is recommended in the following circumstances:

History of anaphylactic reaction, for which epinephrine was required during resuscitation, AND where repeated exposure to the allergen cannot be excluded.

Generalised allergic reactions in patients considered at high risk should a further reaction occur, because of:

- Asthma, particularly if difficult to control
- Limited access to medical care
- Reactions occurring to trace amounts of allergen
- Allergens associated with a high incidence of severe hypotensive reactions such as venom in adults

Severe venom allergy, even following apparently successful desensitisation.

Idiopathic anaphylaxis.

Prescription of epinephrine for self-administration may be recommended in the following circumstances:

Patients with reactions to allergens associated with a high frequency of severe reactions such as nuts, shellfish etc.

Patients who have had generalised reactions and who have other co-morbidities (such as asthma and cardiovascular disease), which may increase the risk associated with an episode of anaphylaxis.

Prescription of epinephrine for self-administration is not recommended in the following circumstances:

Asthma, in the absence of systemic reactions to allergens.

Positive allergy tests (skin prick tests or allergen specific IgE) in the absence of clinical evidence of reactivity.

Positive family history of anaphylaxis only.

Drug allergy is a complex area and an epinephrine autoinjector is rarely required, as allergen avoidance should be possible with appropriate patient education. While there are exceptions, self-administered epinephrine should not be prescribed in the absence of specialist advice.

Generalised rash in response to stings in children.

Patient not willing to carry the device or unable to learn when and how to use it.

Resolved food allergy- when the food has been successfully reincorporated into the diet following a negative challenge. However, individual risk assessment should be undertaken by the patient's immunologist/allergist.

Responsibilities of the prescriber

Epinephrine for self-administration should only be prescribed as part of a comprehensive management plan. As with all prescribed medications, the clinical responsibility for safe administration of the drug rests with the prescriber. It may be helpful to consider the following responsibilities:

- Ensure that patient is aware that allergen avoidance is the mainstay of treatment, and that availability of epinephrine does not replace the need for vigilance.
- Review need for epinephrine both initially and at intervals.
- Review medical co-morbidities relevant to epinephrine use.
- Review medications and if necessary replace drugs that exacerbate allergic reactions or interact with epinephrine (including ACE inhibitors, tricyclic antidepressants and beta-blockers).
- Optimise asthma therapy and ensure patient aware of the need for on-going compliance, and increased vigilance about allergen avoidance during asthma exacerbations.
- Provide the patient with a detailed emergency plan including information on positioning, antihistamines, bronchodilators and epinephrine where indicated.
- Train patient about when to use the device prescribed and ensure patient able to use the device. Use of a trainer device strongly recommended.
- Ensure patient is aware of the need for medical treatment if epinephrine is used, as further medication may be needed particularly if late phase reaction ensues.
- Ensure that appropriate follow-up is arranged for the patient. Follow-up includes review of technique for using epinephrine device, allergen avoidance and changes in co-morbidities and concomitant medications.

Preparation of epinephrine

There was consensus among the group that an auto-injector with the appropriate dose for the patient was the preferable formulation of epinephrine. Under pressure, during a severe allergic reaction few patients could be expected to draw up adrenaline in the correct dosage. Auto-injectors are available in 300µg doses, suitable for patients over 30kgs, and junior pens, which administer a 150µg dose, suitable for patients weighing between 15 and 30kgs. Auto-injectors are not licensed for children weighing less than 15kgs however expert opinion is divided on their use in children weighing less than 15kg. When a young child requires adrenaline, the only available option is to teach parents to draw up and administer the adrenaline. When tiny doses are required, greater accuracy may be achieved by the use of the more dilute 1:10,000 solution. (Allan Colver, personal communication).

A prefilled syringe containing 1ml of epinephrine at a 1:1000 dilution is available (Aurum Pharmaceuticals, UK), and has a longer needle than the auto-injectors. Despite the risk of over dosage, this option may be preferable in patients with a high body mass index, in whom the limited needle length in the auto-injectors may not allow intramuscular adrenaline administration.[36] Intramuscular administration of epinephrine achieves higher plasma epinephrine concentrations more rapidly than the same dose administered by the subcutaneous route.[38]

An individual risk assessment should be carried out to determine the number of auto-injectors, which are required for each patient. However, there was consensus that a minimum of two auto-injectors should be prescribed for each patient. Twenty percent of Anaphylaxis Campaign members who used an epinephrine auto-injector needed or were given a second dose of epinephrine either by self or an attending medic.[39]

Priorities for the future

The ideal treatment for patients with serious allergies would be desensitisation to the inciting allergen, if this were possible. While desensitisation is routine for patients with venom allergy, unfortunately, this form of treatment is not, and will not be available for food allergy, for some time. However, in the short term there are many research and health care delivery goals that could be of value to patients with severe allergies and their families.

Research is needed to identify better predictors of risk for anaphylaxis. Reliable clinical or laboratory predictors could offer reassurance to the large number of patients at low risk, and allow more targeted prescription of epinephrine.

The majority of reactions occur while eating away from home.[9,39,40] Under current regulations prescribed medications can only be dispensed to an individual. However, if feasible, public availability of epinephrine for use by trained personnel, in public places and particularly in restaurants, could improve urgent care and allay anxiety in patients with food allergy. The American Medical Association endorses a system whereby individual states may legislate for a certification procedure for the use of epinephrine by individuals not licensed by other professional boards, to allow those in positions of public safety (life guards, park rangers etc) administer epinephrine.[41] Public defibrillator use could provide a useful model to assess the feasibility of such an approach.

In Ireland, emergency medical technicians are not permitted to administer epinephrine to treat anaphylaxis. While paramedics are trained to provide urgent care for anaphylaxis, including administration of epinephrine, there are few trained paramedics. Hence patients with severe allergy must be in possession of, and able to administer their own medications until arrival at hospital. Appropriate training of ambulance personnel in the immediate management of anaphylaxis is likely to be of value, as well as

reducing anxiety in those with serious allergies. The need to improve availability of emergency medical personnel trained to administer epinephrine has also been recognised elsewhere.[9]

A major source of stress for parents is ensuring appropriate provision for the treatment of their children's allergic reactions occurring while at school. In an American study, 48 out of 109 school districts (with 798,762 enrolled pupils) reported 115 administrations of epipens over a 2-year period.[42] School nurses feel less confident of treating anaphylaxis than cardiac arrest suggesting there is a clear training need.[43] At present there is no cohesive policy, training programme or support for schools to ensure full integration of allergic students into all school related activities. It is currently left to parents to negotiate with individual school Boards of Management (largely composed of volunteers), which have no support in ensuring appropriate provision for the children. Development of model policies, first aid training for school personnel together with appropriate support to deal with insurance and indemnity issues would ease the burden on schools, optimise provision for severely allergic children as well as easing parental anxiety.

There is a paucity of evidence on which to base decisions about when and how much epinephrine to prescribe, and controlled trials will never be performed. Efforts should be made to collect data to provide information about anaphylaxis, epinephrine use, dosage requirements and safety particularly in groups at high risk for adverse effects of epinephrine, both in Ireland and elsewhere.

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The Immunology Group of Ireland is a group of clinical immunologists, immunology nurse specialists, and trainees from both the Republic of Ireland and Northern Ireland. The group aims to improve awareness of immunological disorders, improve the diagnosis, investigation and management of patients with immunological disorders as well as undertaking research, audit and quality improvement initiatives in these areas.

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