

When should self-injectible epinephrine be prescribed for food allergy and when should it be used?

Richard S.H. Pumphrey

Manchester Royal Infirmary, Manchester, UK

Correspondence to Richard S.H. Pumphrey, Honorary Consultant Clinical Immunologist, Manchester Royal Infirmary, Manchester, M13 0JH, UK
Tel: +44 796 120 3672; e-mail: richard.pumphrey@nhs.net

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Purpose of review

To explore why epinephrine autoinjectors have failed to prevent fatal food anaphylaxis and how this problem might be solved.

Recent findings

Autoinjectors cannot save lives when they are used too late, misused, not carried, or when an inadequate dose is absorbed; food allergy-induced asthma may not respond when asthma management is suboptimal. New markers for severe reactions have been published.

Summary

The fallibility of autoinjectors means that in the management of food allergy, their provision must take second place to accurate identification of the trigger foods, optimal avoidance, and optimal treatment of other medical conditions that make reactions more dangerous.

Keywords

adrenaline, autoinjector, epinephrine, fatal, food allergy

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Introduction

Early studies of fatal and near-fatal food allergy emphasized the need for treatment with epinephrine early in the reaction [1,2] and recommended that those at risk should carry their own epinephrine treatment. This caused problems because patients found it difficult to assemble the needle and syringe, then draw up the correct dose and inject themselves [3], particularly in the panic of an incipient anaphylactic reaction (Table 1) [4–6,7^{*}]. A simple device for epinephrine self-injection was first reported in 1980 [4]. For many years, the availability was restricted and even now it is available in only a small fraction of countries worldwide [5,6]. The EpiPen is now available in Argentina, Australia (1998: 4758; 2006: 35 657 pens prescribed [7^{*}]), Austria, Canada, Denmark, Finland, Germany, Israel, Italy, Japan, the Netherlands, New Zealand, Panama, Portugal, Spain, Norway, South Africa, Sweden, Switzerland, UK, and United States.

Defining the problems and possible solutions

In recent years, epinephrine autoinjectors have become widely available (Table 1). Why has this not solved all the problems confronting those at risk of a life-threatening reaction?

Not knowing how to use the autoinjector

Those who carry an epinephrine autoinjector for food allergy rarely have to use it. Unlike diabetic patients, who

through daily use become experts in the art of self-injection, those carrying epinephrine need some form of regular rehearsal. It became clear that all too often the doctor prescribing an autoinjector did not know how to use it [8^{*}] and made no arrangements for their patients' training [9]. When tested for their ability to use the device correctly, many patients failed at one or more of the steps required for successful treatment of a reaction. Wherever autoinjectors are used, similar problems of training and support have been recognized [8^{*},9,10–12].

Specialist food allergy clinics are now so well aware of this problem that most can support their patients with an ongoing program of autoinjector rehearsal. It is also possible to provide this support in other ways such as nurse-led clinics in District General Hospitals [13]. An audit of patients in our clinics suggests that patients given autoinjectors by general practitioners and nonspecialist pediatricians still too often have no training and no support in the use of their epinephrine [14]. The inevitable conclusion is that all patients with epinephrine for self-treatment should be managed in a system with the infrastructure for such ongoing training; if this cannot be provided within general practice the patient must be referred to a specialist who can provide it. Disappointingly, even then, compliance with the training is imperfect [7^{*},14]. Similar support is needed for those caring for children in schools [15]. Although there is evidence that autoinjectors up to a year or more past their recommended expiry date may still be at least partially effective [16],

Table 1 Availability of Anapen

	2001	2002	2003	2004	2005	2006	2007
UK	1500 ^a	16 000	16 000	18 000	27 000	21 000	32 000
France		19 000 ^a	22 000	56 000	80 000	101 000	68 000
Germany			6000	9000	23 600	27 000	29 000
Sweden			7500	14 000	21 000	30 000	34 000
Ireland			16 000	18 000	23 000	23 000	24 000

Ex-factory sales. Since 2005 Anapen has also been sold in smaller numbers to Poland, Hungary, Czech Republic, the Netherlands, Portugal, Bulgaria, Romania, Austria, and, since 2007, Switzerland.

^a Available on named patient basis prior to approval.

training should ensure that the pen is replaced by its expiry date as deaths have followed the use of time-expired pens (Table 2) [17].

As it has proved difficult to train patients to self-inject correctly, alternative delivery systems have been considered. Experiments in a rabbit model have established the feasibility of fast-dissolving tablets releasing sublingual epinephrine [18]. Epinephrine inhalers might have provided a less frightening alternative to injections but there were problems with stability, poor absorption, and difficulty taking the 20 or more puffs needed without significant hyperventilation [19].

Adverse effect on the quality of life

Food allergy adversely affects the quality of life [20*,21*,22**]. Does the provision of epinephrine self-treatment lessen or worsen this effect? Protagonists claim it is reassuring and improves the quality of life, giving the patient a touchstone to relieve the worry of dying from a reaction. But self-treatment may fail (Table 2) and such

reassurance is misguided. Some authors have raised a note of caution about the assumptions that it must always be good to prescribe epinephrine self-treatment [23,24]. There is some evidence that provision of epinephrine self-treatment may itself have an adverse effect on the quality of life [24].

After proper diagnosis of food allergy, accurate identification of the trigger foods, education about effective avoidance, and optimization of management of other medical conditions that might make reactions more dangerous, it would seem most appropriate to leave the choice whether or not to carry an autoinjector to patients after they have been fully informed of the benefits and risks of all management options; only patients wanting epinephrine self-treatment are likely to carry it when it will be needed.

Not carrying the autoinjector

Three out of every four patients dying from food anaphylaxis have had only minor reactions in the past

Table 2 Autoinjector pen usage and fatalities

Pen use	Fatalities	Details
Correct use	13 ^a	10 patients used one dose, one patient used two doses, and two patients used three doses
Low dose	2	One patient used epinephrine inhaler, one patient used 0.15 mg for a 36 kg child (a further dose had been available but was misused)
Late	5	One patient was found collapsed by husband and then given the pen Two patients left the pens at home and had to fetch it (of which one pen was time-expired) One patient collapsed while waiting in pharmacy queue for the pen to be dispensed For one patient the reason was not known
Misused	1	Jabbed in/out, reinserted but most epinephrine spilt
Misfire	1	The pen would not activate
Unused	8	For one patient, the pen given was for nut allergy but the patient was reacting to latex and did not use the pen [17] Two patients had left their pens elsewhere One patient did not use the pen because the reaction was different from the previous ones Two patients had not replaced their pens after use (one used the day before, the other several years previously) One patient found epinephrine to be out of date and so went to the hospital and died after bolus i.v. injection of epinephrine For one patient the reason was not known
No pen	70	GP is known to have refused a request for epinephrine auto-injector in one case

Since 1992 in the UK, of the 100 (this is by chance the number of such patients on the UK register of fatal reactions, not a selected 100) patients with food allergy whose death was ascribed to anaphylaxis, 30 had epinephrine self-treatment kits (one MediHaler-Epi, two Min-i-jet, four EpiPen Junior, 23 EpiPen).

^a One of the 13 patients had a pen for food allergy but had respiratory arrest 30 min after a tablet (aspirin?) from the bathroom cupboard; this reaction was not thought to have been triggered by food.

[25]; so if given epinephrine, they have very little incentive to carry it or even use their prescription to obtain a pen [26]. Even among those who had been recognized in life as having potentially severe food allergy and who had been prescribed an autoinjector, some did not have their pen with them when they needed it – either because they had forgotten to bring it, forgotten to renew or replace it, or because they had lost the habit having had no reaction for so long (Table 2).

How can these patients be persuaded to carry their pen at all times? One approach has been to educate them of the possible danger of a life-threatening reaction. This creates an ethical dilemma: such threats of imminent death have a >99.9% chance of being unjustifiable because the death rate from food anaphylaxis is so low compared with the population prevalence of food allergy [25]. An argument to support this approach is that even to save one life it is worth prescribing self-injectible epinephrine to 1000 people; the psychological harm done by threats of death by anaphylaxis to the others is usually overlooked despite the evidence of its effect on the quality of life [27]. For this argument to succeed, one needs proof that a widespread prescription of autoinjectors has saved lives but such proof is nearly impossible to obtain. Neither anecdotes of survival nor those of deaths following the use of autoinjectors will be convincing without a large randomized controlled trial because almost everyone with a severe reaction to food will survive without treatment and alternative reasons can usually be found for the failure of the autoinjector to rescue the patient.

The arguments above are based on the assumption that carrying epinephrine is to save lives. If, however, epinephrine self-treatment is to ameliorate reactions that would not have been fatal, the physiological, psychological and social adverse effects need even more careful consideration. An important possible adverse effect is the false reassurance given by carrying epinephrine, which may then fail to rescue the patient from a reaction. Clearly, some patients take extra risks because of this reassurance, resulting in at least one death [28^{••}].

As it is likely that patients will not have their pen when needed, consideration should be given to maintaining a supply of pens at locations with a high chance of food-allergic reactions, such as restaurants, canteens, schools and catered events. In some countries (in the UK since 1997 [29]), it is legal for anyone to inject epinephrine without prescription if this is to save the life of someone with anaphylaxis. Staff training would be needed, however, to ensure such public pens are used appropriately. An analogy might be the provision of defibrillators in airports and other key sites [30]. The infrastructure needed for the safe implementation of this strategy will be costly and unfortunately, because death from food

anaphylaxis is so much less common than cardiac arrest, health economists may find the arguments unconvincing.

Inappropriate use of the autoinjector

Inappropriate use of pens is generally safe but can lead to problems. Injection in finger or thumb is common and leads to ischemia from vasospasm [31[•],32]; this can be reversed by local infiltration with phentolamine. The spring in an EpiPen (Dey Laboratories, California, USA) is strong enough to drive the needle through the bone of a digit [33]. There are many cases where epinephrine has been given by a parent or teacher in response to a child's panic brought on by fear of an incipient reaction. One dose is unlikely to do more than exacerbate the panic, but in some instances the child has been given further epinephrine, in one case leading to tachyarrhythmia lasting hours; what is worse, this child had no evidence of allergy in the circumstances leading to the prescription of the pen.

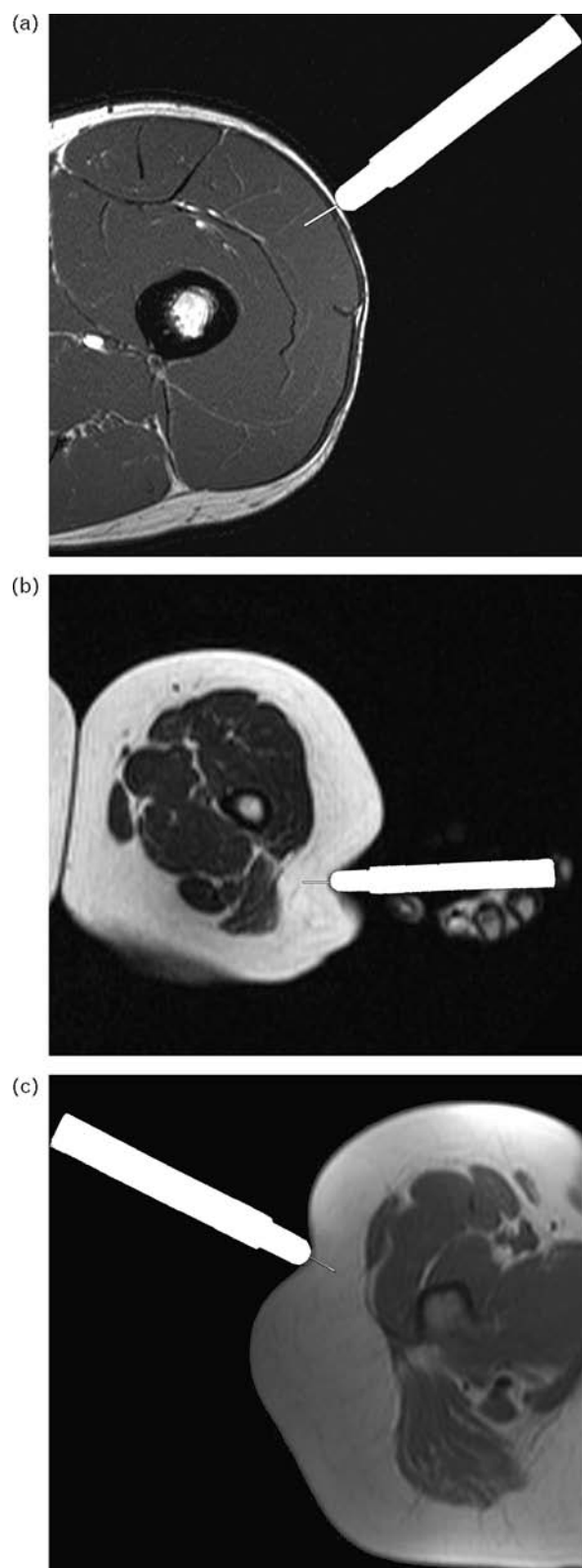
The solution to the problem of digital injection lies either in better patient training or redesigning of the autoinjector. My experience is that injuries from pens activated by pressure on their distal end are less common than those activated by pressure on the proximal end but I can find no published evidence.

Delay using the autoinjector

Fatalities have been blamed on delay in epinephrine treatment. This can happen to patients who have autoinjectors, either because they did not have the pen with them at the time or because they delayed using it in the hope that the reaction would not be severe. The course of a reaction is unpredictable and the escalation of symptoms may be gradual or sudden. Patients commonly find it difficult to know when they should use their pen and their doctors have usually not given them clear guidance – most probably because their doctors did not know the answer to this question either [7[•],11].

So when is the correct time to inject epinephrine? It is common for patients to report recurrent mild reactions with sensations in the mouth or throat or nausea. The patient may be uncertain whether these attacks are really due to a reaction or due to anxiety that there might be a reaction; as described above, use of epinephrine in this situation can worsen the panic and maybe lead to a sensation of difficulty in breathing and hyperventilation. Patients therefore cannot simply be told to inject the epinephrine as soon as they think they may be reacting to a food. Nor can a patient be told to inject if they think they may have eaten a trigger food. The ingredient causing each attack is commonly uncertain, particularly as most patients avoid foods they think will cause a reaction and even in the case of fatal reactions, the final

Figure 1 Magnetic resonance imaging scans of the thigh with superposed silhouette of the trainer pen used to compress the superficial tissues



(a) In a fit teenager, a 16-mm long needle could reach well into the muscle.

analysis may suggest that the trigger was the one that previously only caused minor symptoms. Until the food is analyzed and the sensitivity established, accidental avoidance failure is usually speculative and is therefore unsuitable as a cue for self-injection.

Further, it is not easy to define when is 'too late'. Fatalities have followed early self-injection (for instance, immediately after the nut was seen after biting into a chocolate or as soon as chest tightness followed after accidentally drinking cows' milk); in such cases, we have to look for a different reason for failure of this treatment such as poor absorption, epinephrine resistance, need for a larger dose and so on. On the other hand, when the pen is used after the patient has collapsed with respiratory or circulatory arrest it is easy to blame the failure on the delay.

All these factors lead to the conclusion that it will not be possible to give a simple algorithm suitable for all patients. The evidence that early epinephrine self-injection reduces the need for hospital care following a reaction [34] indicates that patients may often get it right. Patients commonly report that they knew a reaction was going to be bad before the worst of the symptoms started: that might be the right time to self-inject.

Suboptimal injection site

For optimal absorption of epinephrine, the injection must be intramuscular; bolus intravenous injection causes a brief but potentially dangerous surge in blood pressure, subcutaneous injection causes intense vasospasm at the site of injection, locking the epinephrine into the subcutaneous tissues. The extensor muscles of the thigh (vastus lateralis) were found to be a good site for epinephrine absorption [35] and are fortunately also an easy target for self-injection. In animal experiments, however, blood flow through muscles in the presence of epinephrine depends on many factors: exercise and aging lead to opposing effects on the responsiveness to epinephrine of the muscle vasculature [36^{*}] suggesting more work is needed to establish that epinephrine will be equally well absorbed from the thigh muscles in older patients and those with a sedentary lifestyle.

Figure 1 (Continued)

(b) An obese patient with history of anaphylaxis pressing trainer pen onto thigh. Despite detailed training in the clinic, the application of the pen is posterior to the intended target site. The needle would need to be more than 35 mm long to achieve an intramuscular injection. (c) Another patient with a history of anaphylaxis pressing trainer pen onto thigh with muscles tensed in an attempt to compress the adipose tissue and approximate the needle tip to the muscle. This strategy could only be successful in patients with skin-to-muscle distance minimally greater than the length of the projecting needle.

Obesity can also directly affect epinephrine absorption: in lean young patients (Fig. 1a) a 16-mm long autoinjector needle can easily achieve an intramuscular injection; unfortunately the rising tide of obesity means that the needle is commonly too short to reach the muscle (Fig. 1b, 1c) [37]. As this may have been the reason for failure of self-treatment in some fatal cases [28^{••}], it is clearly important that thought is given to providing obese patients with an appropriate means of rescue.

In patients under consideration for epinephrine self-injection, routine measurement of the thickness of the subcutaneous tissue at the target injection site is to be recommended as it often produces surprising results: lean young boys may have pads of fat here, and large ladies may have very muscular thighs with little fat. The very least assessment should be an attempt to assess the skin fold thickness at the target site; this is often difficult to interpret and so assessment by ultrasound or magnetic resonance scan becomes necessary. One possibility for those with too great a depth of subcutaneous tissue would be a postero-lateral injection into the calf muscle (gastrocnemius/soleus); the subcutaneous fat is commonly thin here even in the super-obese and there are no superficial arteries or nerves that might be endangered, but there is no published evidence for rapid absorption of epinephrine from this site. Alternatively, it may be possible to train some of these patients to use a preloaded epinephrine syringe with a longer needle, injecting this at the conventional site; even at this site, further experimental data are needed to establish that epinephrine will be reliably absorbed in such patients.

Getting the dose right

The therapeutic range of epinephrine is narrow; underdosage and overdosage are easy. The accepted intramuscular adult dose for self-treatment is 0.3 mg. The same dose is used for children over 30 kg, and 0.15 mg for children 15–30 kg (but see [38^{••}] for discussion of more appropriate dosing). Family treatment of anaphylaxis for children below 15 kg should be arranged by an appropriate specialist who will often conclude that the dangers of overdose from using 0.15 mg are less than the risk of delay and mistakes from attempting to inject a lesser dose using a vial and syringe. It could be helpful if a wider range of doses were available [39] but this would also entail training prescribers to ensure that the correct pen is used.

Elderly patients with food allergy may pose additional problems. If their muscles behave like those of elderly rats [35], absorption of the epinephrine may be delayed. Angiotensin-converting enzyme inhibitors may promote bradykinin-related swelling or increase shock in anaphylaxis by reducing angiotensin II; both these effects may

be relatively epinephrine resistant. Yet these same patients may be more sensitive to the adverse cardio-respiratory effects of epinephrine; if they become severely short of breath on climbing one flight of stairs, caution with the epinephrine dose is needed. A possible solution might be to give them a pediatric dose (0.15 mg) to use first, and an adult dose to use if this first dose was inadequate.

Occasionally, patients report immediate headache and vomiting together with severe palpitations following a use of their autoinjector; these symptoms typify bolus intravenous injection of epinephrine. Intravascular injection using an autoinjector is unlikely ($P < 0.05$) but simple consideration of the distribution of larger veins in the injection site suggests that the occasional injection may end up with the needle tip in a vein. Reports from our patients who have used autoinjectors are consistent with this, suggesting a frequency maybe $\geq 1:100$.

The recommendation of a second dose if the first was not curative within 5–10 min raises the question of how many pens should be carried by each patient. As well as the possible need for a second dose, it is so common for one or more pens to be misused when attempting to treat a reaction that the requirement for three or more pens could be argued. Often further pens are requested so they can be kept at home and at school, or at home and at work: thus it is common for patients to have six or more pens. The correct solution to this may be to have a single pen, carry it at all times and be properly trained in its use. In this context, a pen that can deliver a second dose could be helpful. For those too young to carry their own pen, a second pen at school can be justified.

Factors that can increase the hazard of epinephrine injection

Tricyclic antidepressants such as imipramine and amitriptyline may predispose patients to cardiac arrhythmia at high doses, and at lower doses in the presence of epinephrine. Cocaine, solvent abuse, and refrigerant inhalation also augment the arrhythmogenicity of epinephrine. Although epinephrine has been thought dangerous in combination with monoamine oxidase inhibitors, it has been used successfully to treat anaphylaxis in a patient taking this drug [40]. Beta-adrenergic blocking drugs may markedly increase the surge of blood pressure when epinephrine is injected because they prevent the normal beta-adrenergic vasodilatation in voluntary muscles.

Patients with a tendency to cardiac arrhythmia may have this triggered by epinephrine injection, especially if there is accidental intravenous bolus injection. Before an epinephrine autoinjector is prescribed, the physician should

discuss all such patients with their cardiologist to decide whether any benefits outweigh the risk.

Suboptimal daily asthma treatment

Among those with food allergy, fatal reactions have largely been a problem of teenagers and young adults who take daily treatment for asthma. As with fatal asthma, fatal food allergy has commonly been associated with a recent exacerbation or suboptimal daily asthma treatment [28^{••}] and indeed, most food allergy fatalities have bronchospasm and mucus plugging of the bronchioles as a major component of the fatal reaction [41]. Among those whose self-treatment with epinephrine was unsuccessful are patients using frequent repeat inhalations of their reliever inhaler (short-acting beta-2 agonist) [42]. A possible explanation is that their airways have become resistant to the effects of epinephrine. Before recommending that asthmatic patients carry epinephrine it is essential to ensure their daily asthma management is optimal; in several of the fatal cases, steroid inhalers had either not been used or had recently been discontinued [28^{••}] and so it may be that stepping down asthma management in those with food allergy should be more cautious than in those without.

Can we target autoinjector prescription more accurately?

Various strategies for deciding who should be prescribed epinephrine self-treatment have been published: Newcastle, UK [43], the EAACI Task Force on Anaphylaxis in Children [44[•]], and the Section on Allergy and Immunology, American Academy of Pediatrics [37]. Surveys of pediatricians [45] and physicians show poor knowledge of who should be given an autoinjector. The published guidance takes previous severe reactions, idiopathic anaphylaxis, and a history of asthma as indications for an autoinjector; however, most of those dying from food allergy have not had a severe reaction. Other risk factors are known, including those with low levels of angiotensin-converting enzyme [46[•]] or low levels of platelet-activating factor acetylhydrolase [47[•]] and the nature of the allergen (e.g. walnut and Brazil nut cause more severe reactions than peanut [46[•]], and in the UK, a higher proportion of those with walnut and Brazil nut allergy die than those with peanut allergy). These and other factors may in due course become part of the standard indications for an autoinjector. Patients can be taught to recognize other risk factors for fatal reactions such as the circumstances of exposure (festive eating is more dangerous than routine daily food), exacerbation of asthma or other allergic symptoms [28^{••}], and encouraged to take increased care with allergen avoidance at these times. Reduced chance of exposure is a better strategy than hope of rescue by autoinjector, considering the data in Table 2.

Conclusion

As well as attempting to prevent the rare possibility of a fatal reaction, management of food allergy should minimize the adverse impact of this condition on the quality of life of the other more than 99.9% of patients and their families. The key to successful management is the accurate identification of triggers for reactions, advice on effective avoidance of these triggers, optimization of daily management of asthma, hypertension and any other medical conditions that may worsen the severity of reactions, and finally, if the properly investigated and fully informed patient wishes, the provision of a rescue package that is tailored to that patient's needs and includes ongoing support and training.

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References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 282).

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