

REVIEW ARTICLE

What are the 'ideal' features of an adrenaline (epinephrine) auto-injector in the treatment of anaphylaxis?

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Abstract

Anaphylaxis is a systemic allergic reaction that often involves respiratory symptoms and cardiovascular collapse, which are potentially life-threatening if not treated promptly with intramuscular adrenaline. Owing to the unpredictable nature of anaphylaxis and accidental exposure to allergens (such as peanuts and shellfish), patients should be prescribed intramuscular adrenaline auto-injectors and carry these with them at all times. Patients also need to be able to use their auto-injectors correctly while under high stress, when an anaphylactic attack occurs. Despite this, an alarming number of patients fail to carry their auto-injectors and many patients, carers of children with known anaphylaxis and healthcare professionals do not know how to use the device correctly, despite having had training. Currently available auto-injector devices have various limitations that may impede their use in the management of anaphylaxis. There is also a lack of validated assessment criteria and regulatory requirements for new devices. This review describes the different delivery systems used in currently available auto-injectors and discusses the key barriers to the use of adrenaline auto-injectors, with the goal of identifying the 'ideal' features/characteristics of such devices in the emergency treatment of anaphylaxis that will ensure ease of use, portability and accurate delivery of a life-saving drug.

Anaphylaxis is an acute multisystem allergic reaction (1) that causes potentially life-threatening cutaneous, respiratory and cardiovascular symptoms and signs such as angioedema, throat tightness, difficulty in breathing, cardiovascular collapse and hypotension (2). Recently, the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network convened a meeting to agree on a definition of anaphylaxis and criteria for its diagnosis. Key outcomes of this meeting included consensus agreement on the definition of anaphylaxis as 'a serious allergic reaction that is rapid in onset and that may cause death' (3, 4). Diagnostic/clinical criteria for accurate identification of anaphylaxis were also set out (3, 5, 6).

Epidemiology of anaphylaxis

Despite the establishment of clinical criteria for anaphylaxis, it remains difficult to ascertain the true frequency of anaphylaxis because patients vary in the symptoms with which they present, and whether they end up in clinical care. A recent review of the available epidemiological evidence has estimated a lifetime incidence rate of 50–2000 episodes per 10 000 persons (i.e. 0.05–2%) (7, 8). Annual incidence rates

vary between countries. For example, in the United Kingdom (UK), it has been estimated that the annual incidence of anaphylaxis is 10.2 per 100 000 (9, 10), and approximately 1 in 1333 of the population of England has experienced anaphylaxis at some point in their lives (11). The estimated prevalence of severe anaphylaxis ranged from 0.5 to 1 per 10 000 in Switzerland and the United States of America (USA), while in Sweden, Budapest, Barcelona and Bombay a slightly higher figure of 1.5 per 10 000 was reported (12).

Fatal anaphylaxis was reported to occur in 0.65–2.0% of cases of severe anaphylaxis, i.e. 1–3 deaths per million people (12). The estimated death rate from food-induced anaphylaxis in children <16 years of age in the United Kingdom is approximately 1 per 20 million population per year (4, 13). However, food is not the only cause of anaphylaxis. The cause of anaphylaxis remains unidentified in approximately one-third of cases (6) and of those cases with a known cause, food (such as peanuts, tree nuts, fish, shellfish, milk and egg) accounted for one-third of the cases (14–16), followed by stings, medicines and latex as the other common causes (6). Pathogenic mechanisms and triggers have been described in detail elsewhere (5, 16, 17) and are outside the scope of this review.

Management of anaphylaxis

Adrenaline is the drug of choice for the treatment of anaphylaxis (1, 3, 10, 18–20). Anaphylaxis often presents in the community setting. In such an event, patients need to be able to recognize what is happening, rapidly self-administer intramuscular (i.m.) adrenaline, and seek hospital admission for professional help and support. When patients get to a clinical setting, healthcare professionals should carry out rapid assessment of the airways, breathing, circulation and orientation, followed promptly by further i.m. injection of adrenaline as necessary (1, 6, 8) (Table 1).

Undoubtedly, the key to successful long-term management of anaphylaxis is to accurately identify and avoid known triggers because most anaphylaxis reactions occur outside a healthcare setting (16, 21). Owing to the unpredictable nature of anaphylaxis, the random occurrence of accidental exposures to allergens, and the short median time to respiratory or cardiac arrest (reported to be 30 min for food- and 15 min for venom-induced anaphylaxis) (22), anaphylaxis is a potentially life-threatening condition and first-aid measures need to be readily available to those affected. Moreover, the possibil-

ity of anaphylaxis has a substantial adverse impact on quality of life if no first-aid package is provided. Therefore, after resolution of the acute episode, all patients should be given at least two adrenaline auto-injectors and trained on how to use them in the event of future episodes (1). In addition, every patient should receive an individualized Anaphylaxis Emergency Action Plan (1, 23).

A systematic review has highlighted the importance of early self-administration of adrenaline because fatalities have been associated with significant delays or failures in administration (8, 24–28). Moreover, early and appropriate intervention with i.m. adrenaline improves outcomes (5, 11, 29–31), while delayed administration of i.m. adrenaline is associated with worse outcomes (6, 8, 15, 32).

If patients have an auto-injector, it is important that they carry it with them at all times (33) because it is impossible to predict when it will be needed. Despite this, 30–70% of patients who had been prescribed auto-injectors did not carry them at all times (5, 34, 35).

Several issues have been identified that may impede the use of currently available auto-injector devices in the management of anaphylaxis (36). The present review describes the delivery systems adopted by currently available auto-injectors and discusses the key barriers to the use of adrenaline auto-injectors, with the goal of identifying the 'ideal' features/characteristics of such devices in the emergency treatment of anaphylaxis.

Delivery systems of currently available adrenaline auto-injector devices

The auto-injector technology currently employed for self-injectable adrenaline devices was originally developed for military personnel and was designed to ensure the rapid and reliable delivery of potentially life-saving medication in time-sensitive, high-stress battlefield situations (37). The pre-measured auto-injector design allows those without formal medical training to use it as it does not require medications to be drawn up via a conventional syringe. This is of great importance, especially in high-stress medical emergencies, such as during an anaphylactic attack, and particularly for children who may find assembling a traditional ampoule/needle/syringe difficult, let alone having to inject themselves.

Currently available auto-injectors require a simple multi-step technique, with instructions printed on the package inserts [reviewed by Davis (37)]. The main difference between the auto-injector devices is in the type of delivery system, which is either cartridge-based or a syringe delivery system.

One disadvantage inherent with syringe delivery systems (Fig. 1) is an extra operational step that requires the needle shield to be detached before removal of the safety cap, followed by thumb activation of the device by pushing a button. An extra operational step may increase the risk of misuse because patients have to memorize and undertake the correct operational sequence at a time of high stress and urgency. After thumb activation, the released spring moves the prefilled syringe to its end position, at which point the needle pierces through the tissue. The piston rod is also

Table 1 Management of acute anaphylaxis in the healthcare setting (adapted from Kemp et al. 2008) (1)

Immediate intervention

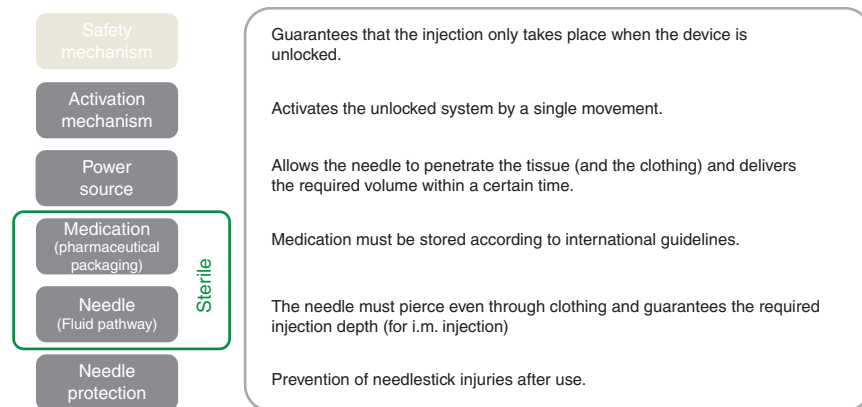
- Assessment of airway, breathing, circulation and adequacy of mentation
- Administer adrenaline intramuscularly every 5–15 min, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock and unconsciousness

Possibly appropriate, subsequent measures depending on response to adrenaline:

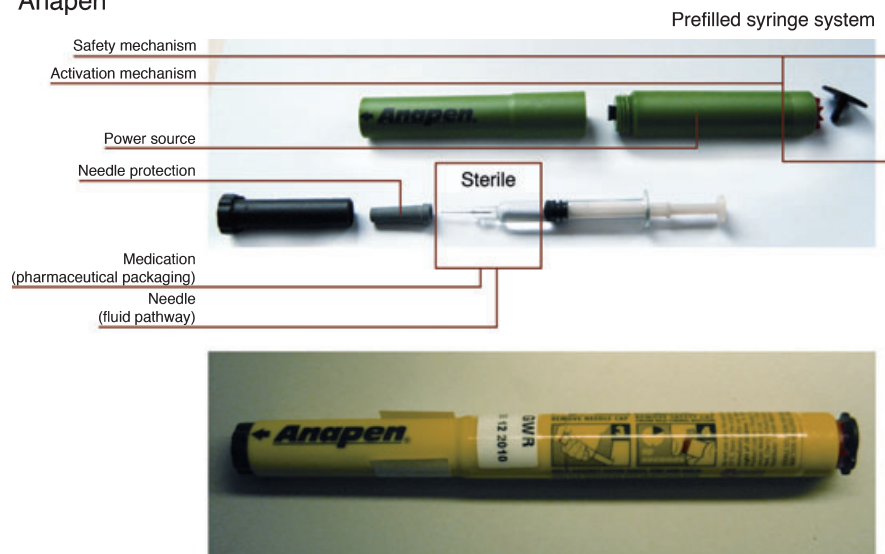
- Place patient in recumbent position and elevate lower extremities
- Establish and maintain airway
- Administer oxygen
- Establish venous access
- Normal saline intravenously for fluid replacement

Specific measures to consider after epinephrine injections, where appropriate:

- Consider adrenaline infusion
- Consider H₁ and H₂ antihistamines
- Consider nebulized β_2 agonist (e.g. albuterol [salbutamol]) for bronchospasm resistant to epinephrine
- Consider systemic corticosteroids
- Consider vasopressor (e.g. dopamine)
- Consider glucagon for patient taking β -blocker
- Consider atropine for symptomatic bradycardia
- Consider transportation to an emergency department or an intensive care facility
- For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary



Anapen



Epipen

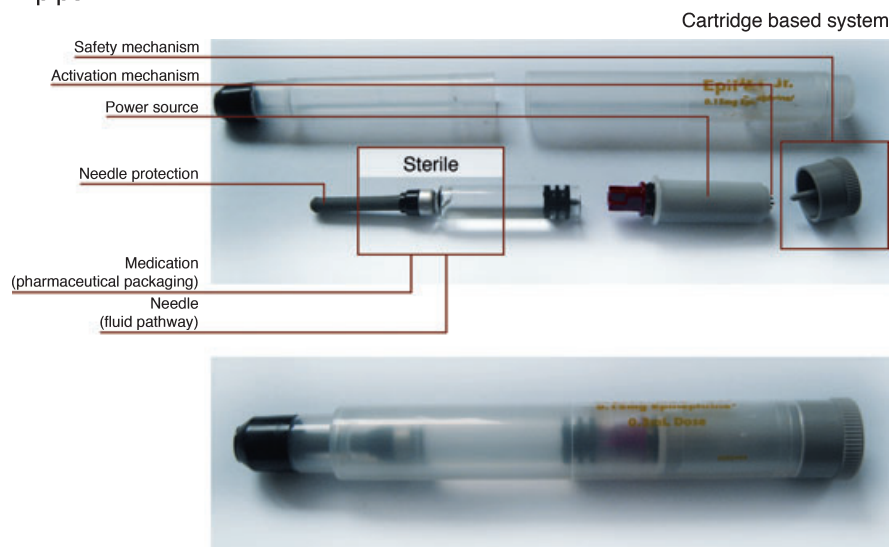


Figure 1 Design overview of currently available auto-injectors for emergency self-administration of adrenaline in the treatment of anaphylaxis.

moved to its end position, and the position of the end stop determines the volume of medication ejected. Therefore, with a syringe delivery system, delivery of adrenaline may start as soon as pressure is applied to the piston rod. This may result in deposition throughout the needle track, resulting in loss of some or all medication before reaching the target muscle.

The effective penetration depth is a component of spring force applied, needle length, bore diameter and how easily the tissue is penetrated by the adrenaline solution. The glass syringe is a limiting factor in the design and limits the force that can be applied by the spring compared to cartridge-based systems.

In contrast, with a cartridge-based device, after the safety cap has been removed, the injector is activated by holding the outer housing and pressing the device tip onto the tissue, allowing the outer housing to move against the inner housing (black tip; Fig. 1). After activation, the released spring moves the cartridge and the attached needle to its end position, which then pierces through the rubber closure and into the tissue. Because of the high power of the remaining spring force, the sealing disc of the cartridge (closure) bursts and opens the fluid pathway. Only then is the adrenaline released. The ejected volume is determined by the end stop on the attached piston rod. Therefore, in addition to having one less operational step, the adrenaline is only released once the needle is fully deployed into the tissue. This helps to ensure minimal loss of medication and delivery of adequate levels of medication to the correct location (i.e. intramuscularly).

A further advantage inherent within a cartridge-based device is the compression force that is associated with the operation sequence of the device. Application of an adequate activation force applied to the device and maintaining this throughout injection compresses subcutaneous (s.c.) tissue, which results in the needle penetrating deeper within the tissue. An ultrasound investigation into the role of compression has shown that an 8 lb (3.6 kg) activation force decreases the distance to muscle by 25% in women and 19% in men, i.e. the adrenaline can be delivered 25% and 19% deeper than the needle length alone, respectively (38).

Types of currently available adrenaline auto-injectors

Just two adrenaline auto-injectors are currently licensed for use in Europe (EU): AnaPen and EpiPen. AnaPen, based on the s.c. insulin pen Autoject Mini, is a single use, syringe-based delivery system. Three forms of this product are available, named AnaPen 500, AnaPen 300 and AnaPen 150; which contain 0.5, 0.3 and 0.15 mg of adrenaline, respectively. Both AnaPen 150 and AnaPen 300 have been licensed for use in the UK since 2001 and across the EU since 2003, with AnaPen 500 licensed in 2009 (39). EpiPen is a single use, cartridge-based adrenaline auto-injector. The device was released in the EU in 1994 and is available in two forms: one containing 0.3 mg adrenaline and EpiPen Junior, which contains 0.15 mg adrenaline (40). Both AnaPen and EpiPen are also produced as training devices. These are needleless replicas of the actual devices that patients can use to practice using the device with a trainer (39, 40). However, these

current training devices only replicate the sequence of administration steps and do little to provide the patient with any of the sensation of an injection by auto-injector.

A third adrenaline auto-injector, TwinJect, is available in the USA only. TwinJect is a syringe-based device that, unlike AnaPen, contains two doses of adrenaline. The first is injected in the traditional manner. To access the second dose, the patient unscrews the needle end of the device and removes the adrenaline-filled syringe from within the device. If symptoms have not improved within 10 min of their first injection, the patient can manually inject this second dose into their thigh. Two forms of this device are available: one containing 0.3 mg and the other containing 0.15 mg adrenaline (41, 42).

Problems with the use of adrenaline auto-injectors

Needle phobia

In a retrospective telephone questionnaire survey of children prescribed an EpiPen auto-injector device, they had only used their EpiPen device in 29% of recurrent anaphylaxis reactions (18). This is perhaps unsurprising because a fear of needles/injections is common (43) and indeed has been reported by 21.7% of travellers undergoing vaccination, 8.2% of whom said the fear was unreasonably intense (44). Thus, a new and improved auto-injector device without the needle in prominent view both before and after self-administration may improve the likelihood of it being used when needed.

Incorrect self-administration technique

Having an auto-injector is not enough: patients and carers need to know how to use it correctly (11, 18). However, in studies only a modest proportion of patients (30–44%) who had been prescribed auto-injectors were able to demonstrate correct self-administration of adrenaline (5, 34, 35). In one study, 50 auto-injector users were provided with training devices and instructions, which were either printed on the device (group A) or in the form of patient information leaflet instructions (group B). Overall, 29 (58.0%) participants successfully completed the training injection: 48.1% from group A and 69.6% from group B (P = not significant). Of those who did not inject successfully 28.6% did not remove the safety cap, 19% operated the device upside-down, and 19% administered outside the recommended injection site. Interestingly, after subsequently receiving standard video training, 15 (88.2%) of the patients who initially did not use their device correctly were then able to do so (45).

Perhaps, more disconcerting is evidence suggesting most doctors in primary and secondary care are also uncertain about the correct use of auto-injectors (5, 46). Moreover, when healthcare professionals who teach patients to use these devices were assessed, as many as 79% were unable to demonstrate the correct use of the device (47).

A written survey completed by parents of children with food allergy reported a direct correlation between empowerment and increased comfort with auto-injector use. In addition, a

strong correlation between auto-injector training and comfort with auto-injector use was found, but neither history of anaphylaxis nor knowledge correlated with an increased level of comfort (48). Therefore, the continued education and training by physicians of parents of children and adult patients at risk of anaphylaxis on the use of an auto-injector device is important so that patients become empowered and more confident in using their device in an emergency situation (43, 48).

Incorrect route of administration – suboptimal injection site

Not only is it important to promptly self-administer an auto-injector using the correct administration technique/steps, but the exact location of adrenaline deposition also matters. Significantly faster peak plasma concentrations are achieved via the i.m. route (8 ± 2 min) than the s.c. route of administration (34 ± 14 min; $P < 0.05$) in children (49) and in adults (50). Therefore, the universally recommended route of administration of adrenaline is an i.m. injection into the lateral aspect (anterolateral) of the thigh (19, 31).

Despite this, there is evidence of the suboptimal delivery of adrenaline. A study examining the sufficiency of the needle length of EpiPen (cartridge system) in penetrating muscles of adults found that many women (42%) had skin-to-muscle distances greater than the needle length alone (38). This was less of a problem for men (2%). Similarly, a study in children 1–12 years of age found that the needles of two currently available auto-injectors (EpiPen and Twin-Ject) were too short to reach the muscle in 12–30% of children (31). Therefore, in terms of needle length alone, use of these devices in many women and children may result in s.c. rather than i.m. deposition (31, 36, 38), although it must be acknowledged that these studies did not take account of subcutaneous tissue compression or extrusion forces on the final site of deposition. With the rising rates of obesity worldwide in both adults and children, there is a need for a new and improved auto-injector device that can guarantee delivery of adrenaline by the recommended i.m. route (31). This may be achieved in new devices by employing an effective combination of factors, such as transmission of the appropriate force to compress subcutaneous tissue at the injection site, suitable needle length and adequate extrusion force to deposit the adrenaline in the muscular compartment.

Needle-stick injury

A total of 59 published cases of needle-stick injury have been reported in the US since 1985 (51, 52). A recent systematic review of the hazards of unintentional injection of adrenaline from auto-injectors concluded that the true rate of occurrence of unintentional injection is probably increasing (53). Indeed, a retrospective review of unintentional injections reported voluntarily to the American Association of Poison Control Centers and the US Food and Drug Administration (FDA) found that between 1994 and 2007 there were 15 190 needle-stick injuries from adrenaline auto-injectors. Overall,

60% of injuries occurred between 2003 and 2007, and patients experiencing unintentional injection had a median age of 14 years (54). These data suggest that additional training may be required regarding the correct use of adrenaline auto-injectors, particularly among younger patients. This is supported by one study that found when patients were asked to demonstrate the use of an auto-injector using a demonstration device, 50% used it in such a way that accidental injection into the fingers would have resulted (55). Possible solutions to the problem of digital injection lie in better patient training or redesigning the auto-injector (53, 56), e.g. to include a needle shield.

Poor absorption and adrenaline resistance

Even after early self-administration of adrenaline, anaphylaxis may have a fatal outcome. This may be because of a number of different factors, such as poor absorption, adrenaline resistance or the need for repeated doses (56). One retrospective study concluded that of the 105 anaphylactic reactions included in the analysis, 36% required more than one adrenaline dose to resolve the allergic symptoms (57). More recent studies have found that between 12% and 19% of food-induced anaphylactic reactions were treated with more than one dose of adrenaline similarly emphasising the importance of patients having at least two adrenaline auto-injectors (10, 58).

Outdated auto-injectors

It is critical that patients carry an auto-injector with them at all times, but it is equally important that they carry one that has not expired (5). As the need to use an auto-injector is unpredictable and infrequent, patients may neglect to check their medication and expiration date. There are currently no published data on the proportion of patients with expired auto-injector devices, but an audit of insect sting emergency kits, which contained an adrenaline auto-injector device, reported that more than half of the kits were out of date (55).

Although far from ideal, in situations when the only auto-injector available is an outdated one, authors have advocated this should be used providing no discolouration or precipitates are apparent as these changes would indicate the adrenaline had degraded (59). Therefore, it might be useful for new and improved adrenaline auto-injectors to have an inspection/viewing window or transparent outer and inner housing that allows for the visual inspection of the condition of the adrenaline solution.

Large size of devices

Currently available adrenaline auto-injectors are rather bulky. This is inevitable given the need to provide the robustness required to protect the adrenaline vials from damage and to maintain device reliability in everyday life situations. However, the large size of currently available injectors may hinder the ability of patients to carry the device on their

person at all times. Although slings are available that can be worn across the abdomen and hold the auto-injector, these are not always practical; particularly, in the case of paediatric patients who may feel self-conscious wearing such an accessory. This issue is compounded by the current advice that patients should carry two doses of adrenaline with them at all times (1).

Lack of standardized assessment criteria

There remains a need for the development of universally accepted, standardized and validated assessment criteria for adrenaline auto-injectors. These devices, which provide a potentially life-saving role, do not currently have to undergo any testing to evaluate their ability to function correctly. Such testing should also be evaluated against expected use of the auto-injector. Without these assessment criteria, the ability of adrenaline auto-injectors to function correctly under standard or adverse conditions must be called into question, and the clinical community should be empowered to demand an agreed framework in which to objectively compare and contrast these devices.

Criteria for the 'ideal' adrenaline auto-injector

Based on the problems associated with the use of current adrenaline auto-injectors, there are five criteria that the 'ideal' device should fulfil (Table 2):

1. It must deliver adrenaline to the correct tissue compartment
2. It must deliver adrenaline within the correct timeframe
3. It must deliver the correct dose of adrenaline
4. It must be robust and reliable enough to withstand real-life use
5. It must be easy, convenient and safe for patients or carers to use.

To be effective, a drug must be administered to the correct tissue compartment. In the case of adrenaline auto-injectors, this requires a device that can deliver the correct dose of drug into the thigh muscle of patients across a variety of body types and sizes, and through a range of clothing. The ideal device would, therefore, have a needle length adequate for i.m. adrenaline delivery under a range of circumstances, with sufficient activation and extrusion forces to ensure that muscle penetration is achieved and that i.m. delivery of adrenaline is achieved within seconds, i.e. the quicker the better. In this way, auto-injectors must also be able to deliver adrenaline within the required timeframe – anaphylaxis is a medical emergency that requires prompt treatment as soon as the symptoms of an attack occur. The ideal auto-injector should have a needle bore wide enough to facilitate rapid delivery of adrenaline, as well as to allow clothing to be easily penetrated.

With regard to criteria three and four, the ideal auto-injector must be able to deliver the required dose of adrenaline for any patient and must be robust and reliable enough to achieve this under high-stress conditions. Criterion three requires a device that is available in a range of concentrations and contains multiple doses; while criterion four demands an auto-injector that operates without fail, even after getting wet and being subjected to trauma. It is important to bear in mind that adrenaline auto-injectors are potentially life-saving devices, and as such they must never fail to activate when they are required to do so. The device should also be constructed to allow for as well as withstand storage, such as in a handbag or school bag, to allow immediate access.

Simplicity of use, the fifth criterion, enables patients to initiate treatment immediately, without first having to process detailed instructions or carry out difficult coordinated tasks. The ideal adrenaline auto-injector should, therefore, have a safety cap that is easy to remove, be easy to activate with minimal activation steps and be intuitive to use with clear

Table 2 'Ideal' features/characteristics of an adrenaline auto-injector

Delivers adrenaline to the correct tissue compartment	Delivers adrenaline within the correct timeframe	Delivers the correct dose of adrenaline	Robust and reliable to withstand real-life use	Easy, convenient, and safe to use
Needle length adequately long	Adequate needle bore and extrusion force to rapidly deliver drug	Available in multiple concentrations	Robust and solid construction	Easy to remove safety cap
Sufficient activation and extrusion forces to ensure subcutaneous tissue compression and muscle penetration achieved	Can easily penetrate clothing	Contains multiple doses	Fit for purpose and able to withstand the rigours of everyday life	Easy to activate with minimal activation steps
	Simple and quick to operate under high-stress conditions			Intuitive to use with clear instructions
	Easily carried and accessible by patients			Needle guard to prevent needle-stick and limit needle phobia
	Robust and solid construction			Injecting end clearly marked
				Integral safety mechanism
				Unable to fire spontaneously
				Able to visibly check adrenaline solution
				Latex-free construction
				Long shelf-life and high stability at a range of temperatures

instructions. For those with needle phobia, the design can help overcome such fear by, for example, introducing needle guards that cover the needle before and after use. As well as being simple to use, the ideal adrenaline auto-injector must be safe, with low levels of risk of needle-stick injury. This can be achieved through several simple design features including clearly marking the injecting end of the device, introducing a needle guard, preventing spontaneous firing via a safety mechanism, allowing patients to visibly check the adrenaline solution, making the device latex free and utilising an adrenaline solution with a long shelf-life and high stability at a range of temperatures.

The aim of developing an ideal adrenaline auto-injector should be supported by universally accepted, standardized assessment criteria. Assessments may include validated tests to determine the functional performance of devices under standard and simulated 'real-life' conditions and to objectively measure all current and potential devices based on the five criteria listed earlier. To obtain regulatory approval and licensing, these devices should be benchmarked to demonstrate attainment of an agreed standard by proving sufficient performance levels in such tests. Most importantly, we need to achieve consensus between manufacturers, clinicians and regulatory bodies (MHRA/FDA, etc.) on such assessments and ensure adoption by all parties.

Furthermore, to maximize safety and ensure correct injection technique effective training and refresher courses should be provided for, and attended by, front-line staff and patients/carers. For effective use in the field, appropriate measures to identify and assist all at-risk individuals should be developed and implemented as part of an improved service provision and overall Anaphylaxis Management Plan.

Novel adrenaline auto-injectors and routes of delivery

Several new devices (Table 3) and alternative delivery systems are currently being developed. Note that all information on these novel devices contained herein has been gathered from the public domain. Hence, the features of the devices described are currently only under development by the manufacturers and have not yet gained regulatory approval. Therefore, if a licence is granted, the final device may not match those described elsewhere.

The first of these novel devices, named Adrenaclick, is based on the TwinJect device, but contains only a single dose of adrenaline. Adrenaclick uses a so-called press and hold activation technique, which requires the user to press the device hard into their thigh and to hold it there for ten seconds. Adrenaclick also features clearly labelled caps, a red injector tip and colour-coded instructions on the side of the unit. However, patients still need to remove two caps before the device can be activated (60).

EpiCard is a second new adrenaline auto-injector, which focuses on reducing the size while maintaining safety and ease of use. Indeed, EpiCard is a credit card-sized device and has the thickness of small mobile telephone, making it easy to carry. Adrenaline is administered by removing the device cover and pressing the auto-injector against the thigh. This

Table 3 Novel adrenaline auto-injectors and their key design features

Device name	Key features
Adrenaclick (60)	'Press and hold' administration technique, designed to deliver the full dose of adrenaline to the correct location Clearly labelled caps Red injector tip Colour-coded instructions printed on the side of the device
EpiCard (61)	Focuses on size, safety and ease of use Credit card-sized device and the thickness of a small mobile telephone Cannot be activated until cover removed Needle immediately retracts after activation to lessen the risk of needle-stick injury Viewing window on device confirms dose administered Recorded verbal instructions played upon activation of the INT02 device
Next Generation Auto-injector (62)	Ergonomic grip to facilitate injection Brightly coloured orange tip for easy identification Easy to read, illustrated instructions on the device One-step, flip-top carrying case for device protection In-built needle cover to lessen the risk of needle-stick injury

causes the needle to spring into delivery position, activate the injection mechanism and immediately retract the needle, lessening the risk of infection and needle-stick injury. A viewing window on the device provides confirmation of the dose of drug delivered. After use, the device is discarded. Two forms of EpiCard are currently in the latter stages of development: INT01, with a perceived unidirectional injection end and a self-retracting needle, and INT02, a version that also includes the so-called PromptSystem™ – an inbuilt application that talks users through the injection process, by simultaneously activating recorded verbal instructions (61). A recent study compared the INT01 and INT02 forms of EpiCard to TwinJect and EpiPen. Of the 48 patients studied, less than half (46%) of those using INT02 correctly adhered to device instructions. This proportion reduced to 27% for INT01, 12% for EpiPen and 0% for TwinJect. Although 73% of patients expressed a preference to INT02 over the other devices ($P < 0.001$) (62), these data suggest that adding voice prompts is not sufficient to achieve correct auto-injector use in the majority of patients and either a new, simpler system or clearer instruction is required. Even then, this is very unlikely to be a substitute for effective training and refresher programmes.

The Next Generation Auto-injector (NGA) has been designed to include an ergonomic grip, a brightly coloured orange tip, easy to read illustrated instructions, a one-step

flip-top carrying case and an in-built needle cover (63). Other novel adrenaline auto-injectors are being developed although few details of these devices are available in the public domain at the time of writing.

In an attempt to completely eliminate the issues associated with auto-injectors, new routes of adrenaline delivery have been investigated. However, s.c. administration and inhaled adrenaline have been found to be less effective than the current standard i.m. route. Subcutaneous administration, for example, has been shown to lead to delayed and variable adrenaline absorption and is not recommended (49), while the use of inhaled adrenaline in paediatric patients failed to raise blood adrenaline higher than with placebo. The bad taste of adrenaline also discouraged children from taking the correct number of inhalations (64). Sublingual delivery of 40 mg adrenaline, in contrast, has been shown to lead to plasma concentrations that are not significantly different to those following i.m. administration of 0.3 mg adrenaline. The effectiveness of this route of delivery, which completely eliminates the injection issues associated with traditional devices, warrants further investigation and development (65).

Conclusions

Anaphylaxis is a sporadic and potentially life-threatening condition whose optimal management requires avoiding recognizable triggers and a first-aid package that includes adequate access to i.m. adrenaline auto-injectors together with effective training in their use. There are several advantages and disadvantages associated with currently available auto-injector devices that utilize syringe or cartridge-based delivery systems. Evidence suggests there are several clear advantages of auto-injectors that utilize a cartridge system compared with a syringe system, such as a simpler operation sequence, higher activation force and tip activation, producing compression of s.c. tissue plus higher extrusion force (hence deeper effective administration depth), and release of adrenaline only when the needle is fully extended, thereby delivering medication more consistently within the i.m. tissue across a wide range of patients.

However, commercially available adrenaline auto-injectors are each associated with significant flaws, and more research is required to investigate and compare other properties

associated with each of the delivery systems in the treatment of anaphylaxis. These properties include activation force, spring force and delivery location of the medication, as well as the robustness of the device.

Given the many issues associated with currently available adrenaline auto-injectors, there is a clear need for new and improved devices that fulfil each of the 'ideal' features of an auto-injector. Several new auto-injector devices and novel methods of adrenaline administration are currently in development. However, the ability of these improved devices to overcome the issues associated with standard auto-injectors remains to be determined in controlled studies. This also requires the introduction of validated assessment criteria, which are currently lacking and should now be a priority with the planned release of multiple new devices in the coming years.

In parallel to the development of new adrenaline auto-injectors and validated assessments, regulatory requirements and licensing systems need to be aligned. There exists a lack of clarity regarding the effectiveness of current devices and only through the introduction of defined regulatory standards for adrenaline auto-injectors will clinicians and patients be provided with effective information and guidance on the use of these devices. The effectiveness of adrenaline auto-injectors may be further improved via the introduction of long-term training programmes for healthcare professionals, patients and carers. Standardization of training could be achieved by introducing legislation regarding the colour coding of devices, injection techniques, etc. which would ensure that everyone who uses an adrenaline auto-injector would do so in the same safe and effective manner.

It is hoped that these improvements will lead to i.m. auto-injectors that can be carried around at all times by patients and are easy to use, so that adrenaline is delivered effectively in emergencies, while treatment failures and accidental needle-stick injuries are reduced to a minimum.

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