

REVIEW ARTICLE

Anaphylaxis treatment: current barriers to adrenaline auto-injector use

T. T. Song¹, M. Worm² & P. Lieberman³

¹Department of Medicine, Allergy and Immunology, University of Washington, Seattle, WA, USA; ²Department of Dermatology and Allergology, Charité – Universitätsmedizin, Berlin, Germany; ³Department of Medicine & Pediatrics, University of Tennessee College of Medicine, Memphis, TN, USA

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Correspondence

Dr. T. Ted Song, Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, 11307 Bridgeport Way SW #200, Seattle, WA 98499, USA.

Tel.: +1 253 589 1380

Fax: +1 253 589 1786

E-mail: tsong@allergyasthmamass.com

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Abstract

Anaphylaxis is a life-threatening condition that is increasing in prevalence in the developed world. There is universal expert agreement that rapid intramuscular injection of adrenaline is life-saving and constitutes the first-line treatment of anaphylaxis. The unpredictable nature of anaphylaxis and its rapid progression makes necessary the availability of a portable emergency treatment suitable for self-administration. Thus, anaphylaxis treatment guidelines recommend that at-risk patients are provided with adrenaline auto-injectors (AAIs). Despite these clear recommendations, current emergency treatment of anaphylaxis continues to be inadequate in many cases. The aim of this review is to highlight the barriers that exist to the use and availability of AAIs and that prevent proper management of anaphylaxis. In addition, we review the characteristics of all AAIs that are presently available in Europe and the USA and discuss the need for regulatory requirements to establish the performance characteristics of these devices.

Although long recognized as a serious disorder (1), the definition of anaphylaxis as 'a serious allergic reaction that is rapid in onset and may cause death' was only recently derived (2, 3) and agreed upon by clinical experts (3–5). Anaphylaxis affects all ages and can manifest with multiple symptoms, involving several organ systems, including the skin, respiratory and gastrointestinal tracts, and cardiovascular system (3). It has been classified into four grades of severity (6), with grades 3 and 4 being severe anaphylaxis, which includes cardiovascular collapse, cardiac arrhythmia and severe bronchospasm (grade 3) and circulatory failure, cardiac and/or respiratory arrest (grade 4). Fatal anaphylaxis has been considered to represent grade 5 (7). Common causes of anaphylaxis are food, insect stings and medicines (8, 9). Anaphylaxis is due to the sudden systemic release of inflammatory mediators from mast cells and basophils. Although the mechanism of anaphylaxis usually involves IgE-mediated activation of mast cells and basophils, non-IgE-mediated mast cell and basophil activation may cause what is often referred to as an 'anaphylactoid reaction', which presents identical clinical symptoms requiring the same treatment (10, 11).

Prevalence

There is evidence that anaphylaxis is under-diagnosed (12) and that it is increasing in prevalence (13, 14). In 2006, a group of international experts used published epidemiological data (13) to conclude that the prevalence of anaphylaxis was as high as 2%, with an estimated frequency of 50–2000 episodes per 100 000 persons or lifetime prevalence of 0.05–2.0%, but with the provision that there was probably significant under-diagnosis. A US nation-wide survey of emergency departments (in 1993–2004) (15) revealed an average of 1.03 million cases per year of allergy-related emergency department visits, representing a mean annual incidence of 0.38% of the US population. Lin et al. (16) conducted an analysis of New York state hospital admissions (in 1990–2006) of patients aged <20 years with an allergic disease as the primary diagnosis. The hospitalization rate for anaphylaxis increased more than fourfold during the studied period (from 1/100 000 to 4.7/100 000). In a similar nation-wide analysis (Australia National Hospital Morbidity Database) (17), for the period 1993–2005, there was a continuous increase in the

rate of hospital admissions for anaphylaxis of 8.8% per year (Fig. 1), with a particularly steep increase in food-related anaphylaxis among children aged <5 years. A study in UK (18) revealed that, from 1991 to 2004, prescriptions for anaphylaxis increased 12-fold.

Rapidity of onset and life-threatening nature

During anaphylaxis, the sudden systemic release of inflammatory mediators can lead to cardiac or respiratory arrest (3, 19) and be fatal if not treated promptly (20). Cardiac arrest can be caused by the direct cardiac effects of the anaphylactic mediators or by shock due to peripheral vasodilatation and increased vascular permeability. Respiratory arrest is as common a cause of anaphylaxis-induced fatalities as cardiovascular shock or cardiac arrest (21) and can be caused by asthma or upper airway obstruction due to pharyngeal or laryngeal oedema, which may also lead to cardiac arrest. Cutaneous and mucosal manifestations are the most overt and frequent signs of anaphylaxis but are absent in 10–20% of cases (22), which may partly explain the under-diagnosis of anaphylaxis. The rapid onset of anaphylaxis is best illustrated by published data obtained from a UK register of fatal anaphylactic reactions (23). This report reviewed the period 1992–1998, during which 130 fatal cases of anaphylaxis were recorded of which 56 had post-mortem (PM) reports. These PM reports revealed how rapidly respiratory or cardiac arrest occurred after exposure to allergen and the onset of a reaction. Respiratory or cardiac arrest occurred with a median time of 30 min after ingestion of food allergen, 15 min after insect stings and 5 min in iatrogenic reactions. Fatalities are estimated to occur in 0.65–2.0% of cases of severe anaphylaxis, accounting for perhaps one to three deaths per million people (7). The incidence of fatalities from food-induced anaphylaxis in children aged <16 years in the UK is about one per 20 million per year (2).

Unpredictability

Allergen avoidance is the optimal protective strategy against anaphylaxis, but unexpected allergen exposure remains a

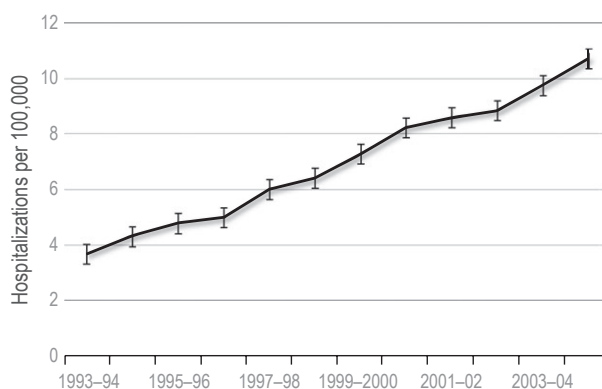


Figure 1 Hospital admissions for anaphylaxis (per 100 000) in Australia (adapted from published data from a national register from Poulos et al [17] with permission).

hazard, particularly in cases due to food allergy (24) and insect sting (20, 25), which are two of the most common causes of anaphylaxis. There is also crucial evidence that a high proportion of individuals experiencing fatal cases of anaphylaxis have had no previous anaphylactic episodes (21, 26). Pumphrey et al. (21) reported the following rates of cases without a prior anaphylactic event among fatal cases: 23/34 fatal cases of anaphylaxis to insect sting, 17/24 to antibiotics, 17/20 to muscle relaxants, 4/6 to nonsteroidal anti-inflammatory drugs, 13/13 to other drugs and 10/10 in contrast media-related anaphylactic deaths.

Emergency management

Immediate intramuscular (*im*) injection of adrenaline is the first-line treatment for anaphylaxis (5, 19, 22, 27). A rapid increase in systemic adrenaline directly counteracts anaphylaxis-induced cardiovascular, respiratory, cutaneous and subcutaneous manifestations (28, 29). It can be life-saving (30), and delayed injection of adrenaline is associated with increased risk of fatality (8, 31, 32), as demonstrated in both insect sting- (31) and food-induced anaphylaxis (32). The World Allergy Organization (WAO) has consistently emphasized the need for prompt injection of adrenaline (33). The joint American Academy of Allergy, Asthma and Immunology (AAAAI) and American College of Allergy, Asthma and Immunology (ACAAI) guidelines (19) state that prompt recognition of the signs and symptoms of anaphylaxis with immediate treatment is crucial to reduce the severity of the systemic reaction, and that, if there is any doubt, it is generally better to administer adrenaline. Also, it is important to note that there are no absolute contraindications to the prescription and utilization of self-injectable adrenaline (34).

Experienced clinical management of anaphylaxis will often not be available to a patient suffering an anaphylactic reaction, not only with noniatrogenic anaphylaxis but also in the clinic where the attending physician may not have previously seen such a reaction (23). There needs to be increased awareness, in the clinic and in the community, that adrenaline is the first-line therapy for anaphylaxis and that adrenaline auto-injectors (AAIs) facilitate a rapid and accurate injection of intramuscular (*im*) adrenaline before specialized medical care is available.

For emergency anaphylactic treatment, AAIs were first introduced in the mid-1990s (35). They are intended to accurately deliver a fixed dose of *im* adrenaline (35) and should ideally be convenient to use and reliably deliver sufficient adrenaline to the systemic circulation (36–38).

Barriers to proper management of anaphylaxis

Despite broad agreement across the various guidelines on the use of adrenaline for anaphylaxis treatment, there is clear evidence that it is not being employed judiciously. In the following, we review the evidence that specific barriers exist that significantly impede an adequate emergency management of anaphylaxis.

Limited awareness of the treatment of anaphylaxis by health professionals

Data from several cohort studies illustrate the extent of under-treatment of anaphylaxis and the low rate of adrenaline use (12, 15, 39–41), with most cases of anaphylaxis that require hospitalization not receiving an AAI on discharge. Adrenaline is much less commonly used than antihistamines and corticosteroids in treating anaphylaxis despite both antihistamines (42) and corticosteroids (43, 44) having an onset of action that is delayed and too late to prevent respiratory and/or cardiovascular arrest, which can occur within minutes (23).

One study compared the effect of three different antihistamine treatments (oral fexofenadine, oral diphenylhydramine and *im* diphenylhydramine) in healthy subjects, given a histamine skin test. The respective mean ($\pm$ standard deviation [SD]) values for the time for a 50% reduction in flare were 51.7 ($\pm$ 17.8), 79.2 ($\pm$ 18.4) and 101 ($\pm$ 12.7) minutes, respectively (42). And corticosteroid treatment is considered to have only a limited role in the treatment of anaphylaxis (45), mainly because of its delayed effects. Corticosteroids may be beneficial in the treatment of the more protracted anaphylactic reactions, particularly for bronchospasm (10, 46, 47), but require up to 4–6 h to reach maximum effect even after intravenous injection (43, 44).

From the anaphylaxis registry that includes 83 centres in Germany, Austria and Switzerland, validated data from 58 of the centres and consisting of 2114 consecutive cases (2006–2010) of severe anaphylaxis were recently analysed (41), to establish the degree of compliance with treatment recommendations. This study revealed that adrenaline was given to only 13.8% of the patients, with just 3.9% receiving *im* injection (Fig. 2). In contrast, 50.1% received antihistamines and 51.3% received corticosteroids. A German nationwide, questionnaire-based cohort study of paediatricians (40) examined all anaphylactic reactions occurring in the previous year. Of a total of 103 children with anaphylaxis, only 17% were prescribed an AAI (41).

Data from several cohort studies in the United States also illustrate the extent of under-treatment of anaphylaxis and the low rate of adrenaline prescription. Using the US National Electronic Injury Surveillance System (NEISS), a nationally representative sample of 20 821 visits at 34 hospital emergency departments was surveyed (12). For a 2-month period (August–September, 2002) and a total of 2333 visits for anaphylaxis, only 19% of patients received adrenaline. Another US nation-wide survey of emergency departments (15) reviewed the treatment of 'acute allergic reaction' requiring emergency treatment between 1993 and 2004. In 12.4 million (1.03 million/year) allergy-related emergency department visits, adrenaline use was infrequent and declined significantly ($P = 0.04$) during the period (from 19% to 7%). Most patients (62%) received antihistamines, and an increasing number (from 22% to 50%; $P < 0.001$) received corticosteroids. An US community cohort study (39) identified, in medical records from 1990 to 2000, that among 134 patients with acute anaphylaxis and attending the emergency department, only 36.6% were prescribed AAIs on discharge.

A recent systematic review (48) documented findings from 59 published studies and revealed a lack of knowledge (in primary care, hospital and community settings) of anaphylaxis diagnosis and treatment resulting in the infrequent use of *im* adrenaline and the failure to prescribe AAIs.

Lack of availability of AAIs for patients at risk of anaphylaxis

Because anaphylaxis is largely unpredictable, occurs as frequently in the community as in hospital, progresses rapidly and is potentially life-threatening, it is essential that all patients at risk of anaphylaxis are provided with an AAI and are made aware of the importance of always carrying it with them. Although AAIs are most often prescribed to patients who have had a previous anaphylactic episode, serious anaphylaxis occurs with significant frequency in individuals who have had no previous severe episode (21, 49). Thus, it is

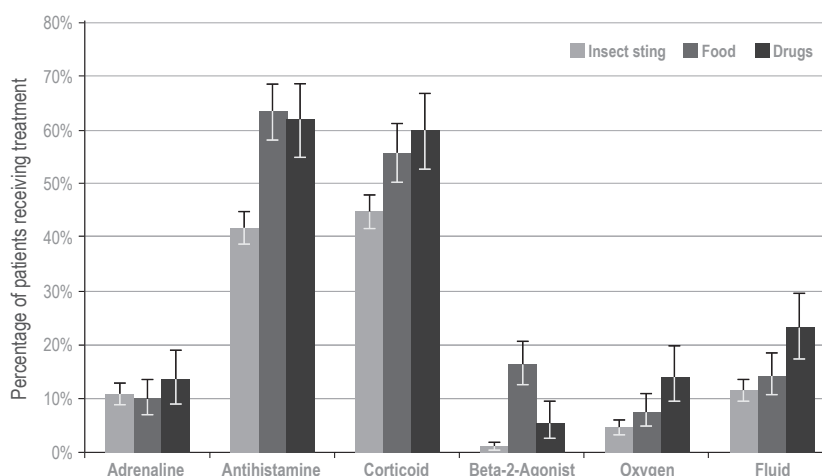


Figure 2 Frequencies of drug administered in emergency treatment of anaphylaxis and separated according to causal allergen

(adapted from Grabenhenrich et al [41] with permission). Error bars indicate 95% confidence limits.

essential to carefully assess the individual allergic patient in order to identify the patient at risk and to provide AAIs not only to those who have suffered a previous allergic reaction to food, insect stings, latex, drugs or other allergen. A significant number of patients who have never suffered severe anaphylaxis are at a significant risk of a future attack. A history of asthma appears to be a major risk factor for severe or life-threatening anaphylactic reactions to food (32, 50–52), and many fatal cases of anaphylaxis occur in allergic patients with asthma (21, 23, 53). Additional risk factors that should prompt consideration of prescribing AAIs include peanut/tree nut allergy, allergic reactions to small quantities of a food, high levels of atopy, food allergy in teenagers and living remote from a medical facility (21, 53, 54).

Expansion of existing national and international databases is expected to refine the quality of data and allow a more systematic approach to identifying the patient at risk of anaphylaxis and requiring an AAI (55). The European Academy of Allergy and Clinical Immunology (EAACI) has released a public declaration on food allergy and anaphylaxis that emphasizes that patients at risk of anaphylaxis must carry AAIs (56). The EAACI is campaigning for food allergy and anaphylaxis awareness (http://webr.emv2.com/eaaci/EAACI_Anaphylaxis_Flyer_English.pdf, accessed on 6 December 2013) and states that at-risk patients are not only those who have experienced a severe allergic reaction in the past but also those who (i) have suffered an allergic reaction after eating a very small amount of food or on skin contact, (ii) have concomitant asthma and food allergy or (iii) have had an allergic reaction after eating eggs, milk, nuts, seeds, shellfish, fish or fruit. Increasingly, national authorities are working with AAI manufacturers to modify AAI prescription information in order to reflect the need to provide AAIs to all at-risk patients and not only to those with a previous anaphylaxis. For example, the EpiPen® has just been approved for use in a number of European countries for patients at risk of anaphylaxis (personal communication from the manufacturer), which is in agreement with the indications that were established several years ago in the United States.

Guidelines indicate that a second adrenaline dose may be needed if symptoms are ongoing or progressive 5–15 min after the first injection and so recommend prescription of two AAIs (19, 22, 27).

Lack of availability of AAIs in public spaces

Because an immediate adrenaline *im* injection can be life-saving (30), there needs to be a broad awareness in society of the disease and how to provide emergency treatment using AAIs, in a manner analogous to the general awareness of cardiac arrest and the availability of automated external defibrillators in public places. Effective prevention of anaphylactic fatalities requires AAIs in public places, particular in venues attended by many people and where food is consumed, such as schools, airports, shopping precincts, sports stadia and restaurants. Provision of AAI needs to be coupled to educating the general public and, in particular,

venue staff about the signs of anaphylaxis and how to administer AAIs.

The EAACI/GA²LEN expert workforce on allergy in schools has called (57) for ‘a cooperative partnership between doctors, community and school nurses, school staff, parents and the child’ to ensure protection of allergic schoolchildren. They recommend that teachers are trained to recognize signs of anaphylaxis and to use an AAI, which should be made available in all schools. This is a response to evidence of the risk of anaphylaxis in schoolchildren. In the United States, many states have adopted a policy of schools being stocked with AAIs, for use by any student in cases of anaphylaxis. The School Access to Emergency Epinephrine Act is under review for possible implementation nationally (see <http://www.gop.gov/bill/113/1/hr2094>, accessed 6 December 2013). Between 10% and 18% of all food allergy reactions or anaphylaxis are estimated to occur at school (40, 58), and 24% of children with a history of anaphylaxis have their first episode at school (59). In the UK, the anaphylaxis rate is one episode per 10 000 children per year and 82% of such episodes occur in schoolchildren and 61% of schools had one child or more at risk of anaphylaxis (defined as having a history of anaphylaxis or carrying an AAI) (60). Less than half of UK schools with an at-risk child had a teacher trained in its management, and 12% had available adrenaline (61).

Limited access to AAIs due to regulatory and economic restrictions

Adrenaline, as a treatment for anaphylaxis, is listed by the WHO as an essential medicine. However, in many countries, there is a significant lack of availability. In some countries, AAIs are not commercially available (Fig. 3), whereas in others, government agencies do not subsidize funding of AAI prescription costs (62).

A survey of the global availability (38) among members of the House of Delegates the WAO, with more than 38 000 individual members in 39 countries on six continents (and with an unanimous response), indicated that AAIs for use in adults were available in 22 countries, mostly in Europe, United States, Canada and Australia. There was limited availability in Asia, South America and Africa, and AAIs for use in children were available in 17 countries. In 27.3% of the countries, no financial subsidy was provided by government or private insurance to defray AAI prescriptions costs.

Failure to use AAIs by patients

Many patients who have been given AAIs, because of a previous anaphylactic attack, do not carry them (11). It was reported (63) that, at one clinic, 76 of 96 patients with insect venom allergy were given an AAI, but <30% of these patients carried it at all times. Only 22% of the patients said that, after a re-sting, they would immediately use their AAI, and 44% were able to demonstrate proper use of the AAI. In a retrospective analysis (64), only 29% of children with recurrent anaphylaxis were treated with their AAI. In a



Figure 3 The extent of availability of adrenaline auto-injectors (AAIs) worldwide (adapted from data from Simons [38] with permission).

prospective study involving 14 paediatric allergy clinics throughout the UK, the most common reasons given by patients for not using the AAI were ‘thought adrenaline unnecessary’ (54.4%) and ‘unsure adrenaline necessary’ (19.1%). The authors concluded that there is much need for patient education to increase AAI use in anaphylaxis. A similar study in 271 children with peanut allergy (in Quebec, Canada) (65) revealed that 48% of the children did not carry their AAI with them in school. Those children who were more likely to carry their AAI with them at school had been previously administered adrenaline for a reaction (odds ratio [OR], 2.7), were older children (OR, 1.1) or were those living only with their mother (OR, 3.4). These authors concluded that ‘more education is required regarding the importance of a readily available autoinjector’. Marrs and Lack (66) pointed out that, especially among adolescents at risk of anaphylaxis, education may not be enough and that more innovative ways are required to encourage and support self-management of allergy and reduce risk-taking in this group of patients.

Efficiency of AAI: how do they perform?

There are five different commercial AAIs currently available and licensed in Europe and/or the United States (Europe: Anapen[®], EpiPen[®] and Jext[®]; US: Adrenaclick[®], Auvi-Q[™] and EpiPen[®]). They each aim to deliver an *im* dose of adrenaline into the *vastus lateralis* muscle of the thigh.

Given the unpredictable and potentially fatal nature of anaphylaxis, randomized, controlled double-blind trials are impossible to conduct because of practical and ethical reasons. However, there are alternative ways to test AAIs’ performance, such as through human and animal pharmacokinetic and pharmacodynamic studies, as well as by means of

studies on adrenaline delivery time and delivery depth into muscle tissue using animal models. Below we review the published evidence from these types of studies.

Pharmacokinetics

In a randomized, single-blind, single-dose, parallel-group study (67), anaphylactic children ($n = 17$, aged 4–12 years), with a history of severe allergies and systemic anaphylaxis, received from a nurse a single *im* adrenaline injection using the EpiPen[®] or a *sc* injection of adrenaline. The children were not studied during an anaphylactic attack and had not had recent anaphylaxis. Plasma adrenaline concentrations versus time are shown in Fig. 4. The mean time to maximum concentration (T_{max}) was shorter with the EpiPen[®] than with *sc* adrenaline (8 min vs 34 min). The authors reported that 6/8 children injected with the EpiPen[®] AAI had T_{max} values <5 min compared with only 2/9 with *sc* injection. The maximum plasma adrenaline concentration (C_{max}) was 19% higher with the EpiPen[®] than with *sc* injection (2.136 vs 1.802 pg/ml).

In another study (68) in children at risk of anaphylaxis ($n = 10$, aged 5–8 years), the EpiPen[®] was used by the child and T_{max} was 15–16 min, which is some minutes later than when the AAI was applied by a nurse. The authors concluded that children probably self-inject less forcefully and this affected the absorption, to some extent. This illustrates the importance of the application technique and that, in very young children, it may be preferable that an adult makes the injection.

In a controlled, randomized, blinded, crossover trial, the same group confirmed in allergic male adults ($n = 13$, aged 18–35 years) which significantly higher plasma adrenaline concentrations were attained with EpiPen[®] AAI into the

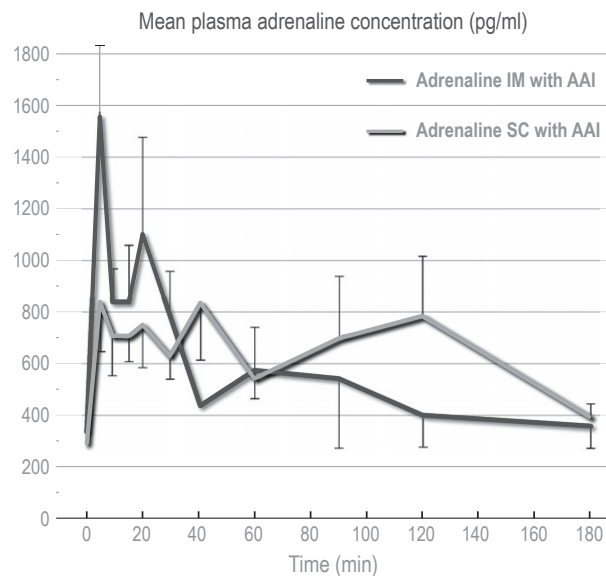


Figure 4 Mean plasma adrenaline concentration plotted against time after intramuscular injection with the EpiPen[®] adrenaline auto-injectors ($n = 8$) or subcutaneous injection of an adrenaline solution ($n = 9$) in children (adapted from Simons et al [67] with permission).

thigh compared with *im* or *sc* normal syringe injection into the arm. A higher mean C_{max} was also observed with the EpiPen[®] into the thigh than with normal syringe injection into the thigh (12.222 vs 9.722 pg/ml; no P -value given).

A pharmacokinetic study in rabbits (69) confirmed rapid systemic exposure to adrenaline with EpiPen[®] *im* injection (T_{max} was 8–9 min). This study also found that adrenaline bioavailability from outdated AAIs was significantly reduced. This illustrates the importance of refilling AAIs once the expiration date is reached and indicates that patients should carry in-date AAIs. However, in case of anaphylaxis, the authors recommend that, if there are no colour changes or crystal formation in an out-of-date AAI, it should be used rather than no adrenaline injection being made.

Only one pharmacokinetic study that compared different AAI devices was found (70, 71). This was a single-dose, single-blind, two-treatment, crossover study, in which 69 healthy subjects received *im* adrenaline injection with the EpiPen[®] and 67 with the Auvi-Q[™]. Bioequivalence of the two AAIs was demonstrated (71), based on the standard pharmacokinetic parameters for bioequivalence assessment, C_{max} , AUC_{0-t} (area under the concentration–time curve from injection to time of last measurement), and AUC_{0-inf} (area under the concentration–time curve from injection to extrapolation to infinity).

Pharmacodynamics

In their adrenaline pharmacokinetic (PK) study, Simons et al. (72) also reported the pharmacodynamic effects of the EpiPen[®]. A pharmacodynamic effect of adrenaline injection

was evident in each subject (Fig. 5), with blood pressure and heart rate increasing over the baseline value. Of note, the increase in blood pressure and heart rate occurred within 10 min after injection, meaning that pharmacodynamic effects correlated closely with the blood levels of adrenaline (C_{max} in 8 min).

No other published studies of AAIs were found that dealt with adrenaline pharmacodynamics.

Adrenaline delivery time into muscle tissue

Pharmacokinetic studies conducted with the EpiPen[®] established that the *im* route is the optimal mode of administering adrenaline for rapid and maximal systemic exposure. Therefore, rapid delivery to the muscle compartment is crucial for rapid systemic availability.

Baker et al. (73) examined whether reducing the duration of *im* injection with the EpiPen[®] below the recommended 10 s would affect the amount of adrenaline injected. This of interest as anxiety associated with self-injection may cause the patient or caregiver to remove the device before 10 s. In an animal model of marbled beef, which has been shown to be of predictive value for injection needle penetration of living human muscle, 21 EpiPen[®]s were tested for the amount of adrenaline injected into the muscle after seven different injection-time periods (1, 2, 3, 4, 5, 6 and 10 s). The authors measured no linear relationship between time and the amount ($P = 0.48$) or percentage ($P = 0.29$; correlation coefficient = 0.464) of adrenaline injected or absorbed into muscle tissue. At all durations, 95.9% or more of the adrenaline dose was absorbed into the marbled beef. The authors concluded that holding the EpiPen[®] in place for 1 s was as effective as 10 s.

No other studies of AAIs were found that tested adrenaline delivery time into muscle tissue.

Adrenaline delivery depth into muscle tissue

Because *im* injection is the best mode of administering adrenaline, AAIs must reliably deliver adrenaline into the muscle, despite variation in the skin to muscle distance between individuals depending on adipose tissue thickness.

One study, using a pig model tested the depth of delivery of adrenaline by the EpiPen[®] (74). It was designed to investigate whether the EpiPen[®], with a needle length of 1.43 cm, propels adrenaline beyond the length of the needle. Methylene blue (0.1 ml) was added, as a coloured tracer, to the 2.0 ml adrenaline solution of the EpiPen[®] before injection into the thighs of pigs ($n = 24$). Dissection of the subcutaneous thigh tissue revealed that the location of the dye was intramuscular after each injection and at a mean ($\pm$ standard deviation) depth of 2.78 (± 0.59) cm, which was significantly ($P < 0.0001$) greater than the length of the needle (see Fig. 6). The EpiPen[®] thus propels adrenaline significantly beyond the needle tip, reaching a depth of around twice the length of the needle (94.4% beyond), which would be enough to reach the muscle even in obese patients. According to the authors, these findings suggest that the delivery of adrenaline beyond the length

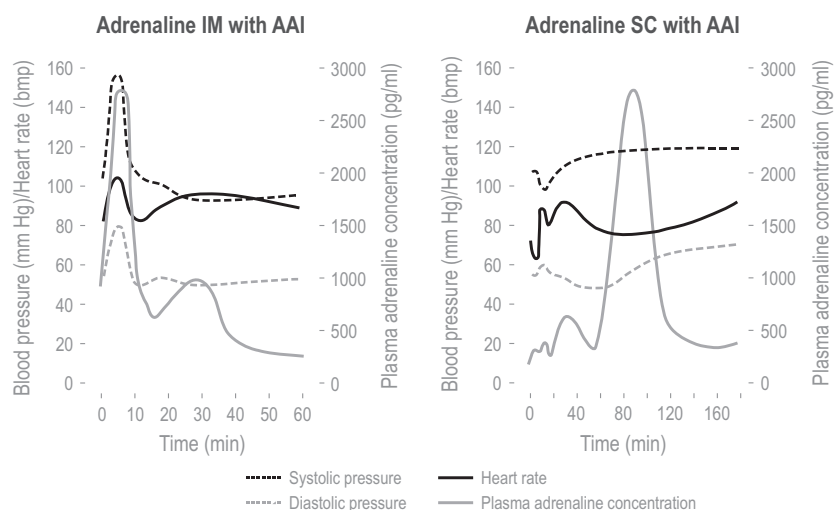


Figure 5 Systolic and diastolic blood pressure, heart rate and plasma adrenaline concentration plotted against time, after intramuscular injection using the EpiPen® adrenaline auto-injectors or subcutaneous

injection of an adrenaline solution (adapted from Simons et al [67] with permission).

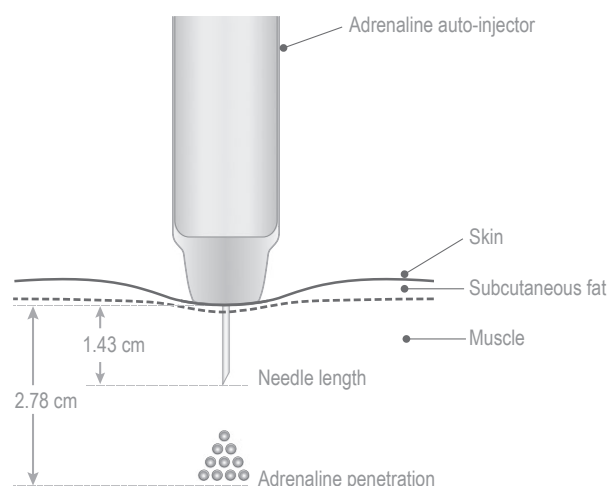


Figure 6 An illustration of the depth of delivery of EpiPen® content of methylene blue after intramuscular injection of pig thigh. Mean adrenaline delivery depth (2.78 cm) is indicated and is nearly twice ($P < 0.0001$) the length of the needle (1.43 cm) (data from Ref. 74).

of the needle is due to both the propulsion mechanism of the AAI and to the compression force exerted on the tissue. The AAIs in this study were applied exerting pressure gradually until they triggered, which implies that the minimum pressure (2 lbs) was applied as they triggered. This suggests that the observed delivery depth is possibly even in the 'worst case' of minimal applied force. The authors conclude from this that with 'more hand swing', as suggested by the manufacturer, would deliver possibly adrenaline even deeper.

A similar study, but *in vitro*, used pork shoulders (37) to compare three AAIs, the EpiPen®, Anapen® and Jext®. A maximal injection depth sufficient to propel adrenaline to

the muscle was achieved with both the EpiPen® and Jext®. However, the Anapen® AAI was unable to inject adrenaline beyond the needle length and failed to consistently reach the muscle. Unfortunately, neither the actual injection depths for the three AAIs nor any statistical analysis were reported; this would have been helpful and should be considered in future studies.

From the above review of the data on AAI performance, it can be seen that it is only the EpiPen for which published data are currently available on the PK, pharmacodynamic, depth of penetration and time to delivery of the total adrenaline dose.

Conclusions

Although recommended by international guidelines and expert groups, the use of AAIs for emergency first-line treatment of anaphylaxis is not often performed. This is due to the existence of various barriers related to clinicians, patients and regulators. The barriers that need to be overcome in order to improve emergency management of anaphylaxis have been reviewed here, and a number of conclusions can be extracted.

There is a need to educate clinicians and patients on the life-saving potential of self-injectable adrenaline. Currently used antihistamines and corticosteroids are not recommended in international guidelines as front-line treatment. There is a particular need for clinicians to learn to recognize at-risk patients, in order to provide them with AAIs and for patients to appreciate the vital importance of always carrying AAIs with them and being prepared to use them without delay at the first sign of anaphylaxis. Clinicians and policymakers need to work together to increase awareness of anaphylaxis and to make AAIs accessible to all patients with prior history and at risk of anaphylaxis. Promoting initiatives to make AAIs available in public places is essential to prevent fatal anaphylaxis.

Despite the recognized importance of AAI for the emergency treatment of anaphylaxis, the available data on their efficiency are surprisingly limited. Although ethical and practical barriers impede testing AAI conventionally by means of randomized trials during anaphylaxis episodes, it is possible to test their performance by other means. Currently, published pharmacodynamics and pharmacokinetics data are available for only two products. There should be open discussion on the need for regulatory authorities to require AAI manufacturers to provide supportive data for assessing the efficiency of new AAI devices before marketing authorization.

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Conflicts of interest

Dr. Lieberman reports acting as a consultant and speaker for Mylan, Sanofi-Aventis, Meda, Teva, Genentech and Merck. Dr. Song has served as speaker for Meda, Teva and Novartis. Dr Worm has served as a speaker for Meda, ALK and Allergopharma and is an active advisory board member.

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