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Anaphylaxis (M Sánchez-Borges, Section Editor)

# Choosing the Optimal Self-Injector Epinephrine

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## Abstract

*Purpose of review* Anaphylaxis is an acute, systemic, life-threatening allergic reaction, and its choice treatment is epinephrine. Epinephrine may be administered by several routes, but intramuscular is the preferred one because of its fast time of action, as well as easy access. Several devices are commercially available for self-administration, with some differences between them. There are concerns about defects or errors in administration when using autoinjectors.
*Recent findings* The main factors that determine the correct use of an autoinjector are the length of needle, body mass index, use of clothing, type of device, and training of the person applying epinephrine. Comparing different devices not only highlights some differences between them; but it also finds the similarities in their effectiveness and defects. There are areas of opportunity in the design and route of administration that may be addressed in future research.
*Summary* This review focuses on devices for treatment of anaphylaxis like autoinjectors and includes analysis of factors specific to the device, as well as those dependent on the patient and who applies the device. The best device will be the one that is available, together with adequate training of patient/caregiver and health personnel for its correct use.

## Introduction

Anaphylaxis is an acute, systemic, life-threatening allergic reaction [1••]. The drug of choice and the first line of treatment of anaphylaxis is epinephrine. Interestingly, epinephrine is not used in all cases of anaphylaxis [2], particularly there is a bias for use in pediatric or elderly patients [3–5]. Late administration of epinephrine may be associated with biphasic reactions [6].

Epinephrine is a catecholamine, a non-selective adrenergic agonist, which stimulates the alpha 1-, beta 1-, and beta 2-adrenergic receptors. Its effect on alpha-1 receptors is to increase peripheral vascular resistance, which causes vasoconstriction and decreases mucosal edema. Stimulation of beta 1 receptors induces a positive chronotropic response and a positive inotropic effect. Stimulation of beta 2 receptors produces relaxation of bronchial smooth muscle [7•].

Although there are several routes of administration, the intramuscular route is the preferred one (doses of 0.01 mg/kg of solution at 1:1000 [1 mg/mL] up to a maximum of 0.5 mg in adults and 0.3 mg in children), in anterolateral portion of the thigh, since it reaches an intermediate time of action of 8 min. Intramuscular syringe application reaches an initial peak of plasma epinephrine concentration at 5–10 min and a higher peak at 50 min. This biphasic response is also observed with the use of autoinjectors [8, 9]. In a multicenter study in which standardized simulations of anaphylaxis were performed, at least one epinephrine-related error was made in 68% of both autoinjectors and manual injections [10].

# Epinephrine autoinjectors

The epinephrine autoinjectors (EAI), available since 1987, are the preferred method of outpatient administration, allowing self-administration, application of a fixed dose, speed of application, consistency in penetration, and depth of the needle. Currently, there are different self-injection devices, but the availability is not universal, and the cost can be high. In a study conducted in 2019, EAI was commercially available in 80% of 25 countries included, and Epipen® was the only device available in 45% of the countries and the most dominant product in 85% [11]. The efficacy and safety results cannot be generalized, as there are variations according to the device, storage conditions, patient-dependent conditions (weight, gender, ethnicity), and the person administering the autoinjector (technical ability) [12–14].

Hill et al. compared 5 different devices (EpiPen® [0.3 mL], EpiPen® Jr. [0.3 mL], Twinject® [0.15 mL, 0.3 mL], and Anapen® 300 [0.3 mL]) with each other and against manual syringe application in an animal model. They found that EAI achieved higher peaks of injection volume than manual injection, with a greater degree of dispersion. When comparing devices, they showed that EpiPen® achieved higher volumes of dispersion and higher initial dispersion rate. The main functional difference between Epipen® and the rest of the devices was the spring force (23 pounds for EpiPen® compared to 6 pounds for Twinject® and 2.1 pounds for Anapen®) [15•].

There are doubts as to whether the intramuscular application will be successful in overweight patients when using an EAI, and whether it will be necessary to manufacture devices with longer needles [16]. Worm et al. demonstrated that a length of the EAI needle of approximately 16 mm was

successful in individuals with a body mass index of 18–40 kg/m$^2$, demonstrating faster absorption and higher levels of epinephrine compared to intramuscular administration with an average 23-caliber syringe (range 22–27) [8]. Duvauchelle et al. compared 10.55-mm needle length application of EAI versus intramuscular application with a 25.4-mm pre-filled syringe, in normal weight and overweight women. They used ultrasound to establish the depth of injection and found that application was subcutaneous in 10/12 of obese women, although the concentrations achieved did not differ from those of normal-weight women [9].

The risk of intraosseous administration in children when using an autoinjector device that requires high pressure (HPI) is greater if the application is on bare skin and is reduced if it is applied on clothing with a thickness of 3 mm (winter clothing), where the group of children weighing < 15 kg has the greatest risk. Devices that require less pressure (LPEAI) have less risk of intraosseous administration; but the risk of subcutaneous administration is increased [12, 13, 17]. Determining by ultrasound the length needed for intramuscular administration of a drug, it was found that patients with higher body mass index have a greater distance to muscle. This trend was greater in the group of African-American female patients compared to white male patients [18]. Manuyakorn et al. demonstrated that in children weighing less than 15 kg, the needle length of EAI devices can be excessive [19]. Overall, there is a large variation in the risk of intraosseous or subcutaneous administration with the use of EAI.

In a web-based survey, Campbell et al. investigated the preference of emergency department healthcare personnel for use of an autoinjector versus manual epinephrine syringe administration for the treatment of anaphylaxis. They found that 82% preferred EAI. Reasons included easy training in its use, speed of administration, less risk of dosing errors, increased risk of self-harm, and cost [20]. Although high costs of autoinjector devices led Emergency Medical Services in the USA to consider, or even switch to, manual syringe injection, it is recommended that such a change be accompanied by an ongoing program of education and training, with constant supervision [21]. Chime et al. found that more potentially life-threatening mistakes are made when using manual syringe injection compared to EAI [22].

Although manual syringe administration is not an ideal option, it is preferable to alternative of not administering epinephrine. In 2017, the FDA approved the use of a pre-filled syringe for manual administration of epinephrine in two forms, 03. mg and 0.15 mg, for patients > 30 kg and 15–30 kg, respectively. In a study of untrained adolescents, ease and safety of use were demonstrated [23]. Another option is to provide the patient with epinephrine ampoule and syringe for administration. It is recommended that the length of the needle be the correct length for intramuscular administration according to the weight/age of the patient. This is the method we use in our center, since in our country there are no autoinjectors available commercially, the patient is given a bag with 2 ampules of epinephrine 1 mg in 1 ml, 2 syringes of insulin 1 ml, 2 needles of 22 G or 23 G, for use in adults or children, respectively. After breaking the ampoule and loading the corresponding dose, the needle should be changed, and the injection applied as described above. It is provided with an instruction manual and a written action plan (Fig. 1).


**Fig. 1.** Anaphylaxis kit. This picture has never been published and the authors have permission to publish it.

An alternative, in countries where there is no access to EAI or commercially pre-filled syringes, and the patient does not feel confident about filling the syringe, would be to prepare the syringe with the corresponding dose of epinephrine; but sterility and stability cannot be guaranteed beyond 3 months or 2 months in climates with high temperatures and low humidity [24, 25].

Also, EAI has care restrictions beyond expiration date; you should follow the manufacturer's recommendations about exposure to high or very low temperatures, as well as avoid exposure to sunlight. It is not recommended to administer an expired device or one that has been exposed to high temperatures, showing precipitation or discoloration [26, 27]. However, there is evidence to suggest that the process for determining the expiration date of EAI should be reviewed, which may extend the life of the device [28].

It is not enough for a device to be effective if proper training in its use is not undertaken; if the device is changed, the physician must ensure that patient/caregiver is aware of the new device [29] and patient/caregiver or healthcare personnel must recognize the symptoms of anaphylaxis [30, 31]. In a study in Turkey, all steps were correctly

performed in 40–60% after a training time of 57 to 90 s [32]. Other studies found that training every 6 months allowed a probability of proper use of 96%, although in another study it was found that, with some devices, after 3 months of training, only 35% of participants were performing the technique correctly [33, 34].

In a systematic review, they found that factors associated with patients' good technique in using EAI included being older than 18 years, being trained by an allergist, severity of anaphylaxis, duration of adrenaline prescription, and belonging to a self-help group. It should be noted that, in this review, the group that showed the lowest percentage of correct technique before training was that of health professionals, with 21% improving to 65% after training, compared to the group of patients and caregivers, with 32–37% pre and 77–79% post-training, which highlights the importance of training health professionals in the correct use of autoinjectors and management of anaphylaxis, in general [35•]. In countries where the pharmacist figure exists, they should also be included in education programs on the identification of anaphylaxis and the use of epinephrine autoinjectors [36–38].

It is recommended that the patient or caregiver carries at least 2 self-injectable devices, as a second dose is required in 20–36% of cases. Situations that require a second dose include not rapid access to medical care, history of previous severe reaction, elevated body mass index, and asthma, as risk factors, in addition to technical situations such as an error in administration, as well as conditions typical of that condition of anaphylaxis (very severe reaction, biphasic response) [39•].

The World Allergy Organization expert group for in-flight treatment of a systemic allergic reaction or asthma exacerbation recommends intramuscular administration of epinephrine, at the dose already described [40]. And a recent publication suggests that EAI may prove to be a valuable tool in treating life-threatening allergic reactions during flight [41].

Among the reasons why patients or their caregivers do not carry self-injectable devices, in addition to cost, are the shape and size of the device, doubts about being able to use it correctly, and forgetfulness [42, 43]. Precision of the instructions may also be a factor in determining patients' preference for one device over another [44].

Recently, animal model studies of intranasal epinephrine use have been published, and results appear promising; but additional information is needed to transpose human experience [45, 46].

## Conclusions

Dispensation of epinephrine should be available to all patients suffering from anaphylaxis, regardless of setting, be it home, school, work, or medical. Patients, caregivers, and health care personnel should be trained to recognize the signs and symptoms of anaphylaxis and know the correct technique and dose of epinephrine administration. An ideal device would be one that is easy to use, small, comfortably designed, even with an alarm or reminder so that it is not forgotten, and perhaps by a different route. But realistically, the ideal device is one that is

accessible, and it is the responsibility of medical personnel to train patients and their caregivers in its use, as well as in the timely recognition of signs of anaphylaxis.

## Compliance with ethical standards

**Conflict of interest**

Alejandra Macías-Weinmann declares that she has no conflict of interest. Sandra Nora González-Díaz declares that she has no conflict of interest. José Ignacio Canseco-Villarreal declares that he has no conflict of interest. Rosa I Guzmán-Avilán declares that she has no conflict of interest. Valeria González declares that she has no conflict of interest. Andrés Noyola declares that he has no conflict of interest.

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- •• Of major importance


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## Publisher's Note