

EDITORIAL

Adrenaline autoinjectors in food allergy: In for a cent, in for a Euro?

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The first-line treatment of food allergy is a thoroughly indicated and performed elimination diet. However, since potentially life-threatening contact with the eliciting food cannot always be avoided (even if families, caregivers, and kindergarten personnel are perfectly educated), provisions for emergency situations are mandatory. The mainstay of an emergency set is an adrenaline autoinjector, which can be used by the patients or surroundings.

Underuse or overuse?

The question has been raised whether there is an adrenaline autoinjector overuse ['EpiPen epidemic' (1)] or whether adrenaline autoinjectors are still under-prescribed and underused. Studies have reported underuse of adrenaline autoinjectors by patients and parents (2, 3). However, the definition of anaphylaxis differs between different countries, and the broader the definition, the higher the reported rate of underuse will be. Therefore, the first step is to agree on a definition of anaphylaxis, which is a severe, systemic allergic reaction with an acute onset and a life-threatening character (4). Secondly, the habit in which patients an adrenaline autoinjector is prescribed or not plays a role. Thirdly, it makes a difference whether the indication to use an adrenaline autoinjector is an existing anaphylactic reaction or an impending status. All these factors mean that the results of these studies of underuse or overuse should be viewed with caution.

Who should be prescribed an adrenaline autoinjector?

Unfortunately, there are still no agreed indication criteria for prescribing an adrenaline autoinjector for patients at risk (5). Table 1 lists proposals for indications.

Table 1 Proposals for the prescription of an adrenaline autoinjector in food allergy

History of an anaphylactic reaction to the corresponding food in the past
Patients with any systemic reaction to a food in combination with bronchial asthma
Systemic allergic reactions to foods with a high risk of severe reactions such as peanuts, tree-nuts, and seeds
Patients who exhibit clinical reactions even to tiny amounts of the food
Patients with underlying mastocytosis and food allergy

Since there is no forensic enforcement to carry an adrenaline autoinjector, the single indication should be discussed with the parents and families, weighing personal advantages and disadvantages. Furthermore, because the decision for an adrenaline autoinjector means round-the-clock preparedness all day, every day of the year, the decision should be based on the medical history rather than a desire on the part of the physician to sleep more easily.

Adolescents may show an enhanced risk for severe allergic reactions for the following reasons:

- 1 In this age group, food allergy is often more severe
- 2 Adolescents have a higher risk behavior
- 3 They do not tell others about their (food allergy) problems
- 4 They do not avoid strictly (enough)
- 5 They treat their asthma badly
- 6 They forget to carry the autoinjector with them
- 7 Alcohol can play a major role as a possible augmentation factor as well as for a lower risk threshold.

How many autoinjectors should be prescribed?

A further consideration is the number of devices, which should be prescribed for a patient (6–8). General indications for prescribing more than one device may be

- 1 high body weight requiring a higher dose than delivered by one device, especially with the relatively low maximum dose of 300 µg available in most countries,
- 2 fear of a possible miss-firing,
- 3 a location without promptly available professional medical help,
- 4 concern that the first shot may not help sufficiently or for long enough,
- 5 protracted or recurrent clinical reactions in the past, and
- 6 persistent bronchial asthma.

Only one device may be required if the patient is able to have the device with them at all times. However, there is no convenient way to carry it so far (especially in small children), and if it is forgotten, no autoinjector would be available during transport or at the destination. Prescribing two or more devices (one for each regular location, for example, at home and kindergarten/school) offers the advantage that a device will not have to be carried at all times, but with the disadvantages of non-availability during transit or at third locations, and higher costs.

In conclusion, the best compromise may be one (or two) adrenaline autoinjectors directly with the patient, because this is most likely to ensure the availability of the device in an unexpected emergency.

When should an adrenaline autoinjector dose be administered?

An important aspect concerns how to educate families and patients about when to administer an adrenaline autoinjector dose. The consensus (currently supported by anecdotal evidence) is to administer adrenaline 'sooner rather than later', that is, as soon as the initial signs and symptoms of anaphylaxis are observed, regardless of their severity, because fatalities in anaphylaxis usually follow delayed or inadequate administration of adrenaline (9).

An adrenaline autoinjector should be immediately used in the event of unconsciousness and/or any kind of audible or visible dyspnea and/or the involvement of two organ systems an adrenaline autoinjector should be immediately used. The situation is less clear-cut, if some hives are observed or the patient is simply vomiting. In this case, it may be helpful to take the following factors into consideration: (i) the time interval between the suspected ingestion and the occurrence of symptoms and (ii) the certainty of the exposure and the general health condition. If symptoms occur within a few minutes after ingestion and the exposure to the eliciting food is likely, the adrenaline autoinjector should be administered immediately. However, if few hives are observed after a doubtful exposure and the patient is in a good general condition, one should keep the adrenaline autoinjector ready to use while closely observing the patient and wait for the progression of symptoms. Individual solutions have to be sought for any situation in between.

Who should be trained?

The decision to prescribe an adrenaline autoinjector implies appropriate training on how to respond in emergency situations. Certainly, the parents and possibly also grandparents or older siblings should be involved. Problems arise with staff at nurseries and schools. While day care staff show a pleasing willingness to take on some responsibility (although they are not legally obliged to do so), many schoolteachers are still very reluctant. Efforts should be made to implement education programs in such institutions. Unfortunately, the problem of financial reimbursement is unresolved in most countries.

Why do patients do not always receive adrenaline when necessary?

Many factors contribute to the low rate of doses administration by patients and those around them even when indicated (10)

- 1 failure to recognize anaphylaxis,
- 2 uncertainty about autoinjector administration technique,
- 3 uncertainty about the indication to use, and
- 4 fear of side effects.

Regular training of patients, families, and surroundings is mandatory. It is often astonishing how quickly people can forget acquired knowledge. Over the counter, autoinjector training devices should be available in each setting the patient's life to repeat skills and expertise.

What should be done after accidental administration in a finger?

There are several possible ways misusing adrenaline autoinjectors; the most important being triggering before the autoinjector is in position or inadvertent injection into other parts of the body, such as fingers (11). Overpenetration of the intramuscular layer may lead to injury of bones and joints (12). Consequences of misuse are not only that the patient will not benefit from the adrenaline therapy, but also possible harm to the administrator and finally waste of money.

The most common mistake is accidental injection into fingers, mainly the thumb, with a consequent risk of ischemia. The worst case is extreme hypoperfusion with demarcation and loss of the finger. However, severe side effects seem to be rare (13). In the event of accidental injection into a finger, the digit should be rubbed in warm water; adequate hydration may also be helpful. Vasodilative treatment (14) is not necessary in most cases (13, 15).

However, it is not known whether this positive outlook for the available doses of 150 µg or 300 µg is also true for higher doses. Efforts are mandatory to train physicians, patients, and contact persons effectively to ensure correct administration and therefore provide optimum help for the patient with a severe allergic reaction. In many countries, education programs have been developed for patients and caretakers. Moreover, train-the-trainer-seminars are under development for physicians (16).

Problems with the shelf life

Adrenaline autoinjectors have a total shelf life of 18–24 months, but patients often complain that the remaining shelf life of autoinjectors handed over by pharmacies is <12 months. This unprofessional storage policy along the supply chain induces additional costs and efforts (i) for patients (they need to care about a new prescription after an unnecessary short interval), (ii) for physicians (impacting on the prescription budget), and (iii) for health insurance companies. So far, there is no satisfactory solution for this problem. Pharmaceutical companies and wholesalers should agree on a more effective logistical strategy.

Conclusions

It is hoped that these considerations and proposals will induce a discussion of the appropriate decision process on the use of adrenaline autoinjectors. Furthermore, they may contribute to a more balanced and assured handling of emergency situations until studies offer more objective information.

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Reference

1. Kemp AS. EpiPen epidemic: suggestions for rational prescribing in childhood food allergy. *J Paediatr Child Health* 2003; **39**: 372–5.
2. Flokstra-de Blok BMJ, van Ginkel CD, Roerdink EM, Kroeze MAJM, van der Meulen GN, Dubois AEJ. Extremely low prevalence of epinephrine autoinjectors in high-risk food-allergic adolescents in Dutch high schools. *Pediatr Allergy Immunol* 2011; **22**: 374–7.
3. Noimark L, Wales J, Du Toit G, et al. The use of adrenaline autoinjectors by children and teenagers. *Clin Exp Allergy* 2012; **42**: 284–92.
4. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; **117**: 391–7.
5. Sicherer SH, Simons FER. Self-injectable Epinephrine for First-Aid Management of Anaphylaxis. *Pediatrics* 2007; **119**: 638–46.
6. Manivannan V, Campbell RL, Bellolio MF, Stead LG, Li JTC, Decker WW. Factors associated with repeated use of epinephrine for the treatment of anaphylaxis. *Ann Allergy Asthma Immunol* 2009; **103**: 395–400.
7. Järvinen KM, Sicherer SH, Sampson HA, Nowak-Węgrzyn A. Use of multiple doses of epinephrine in food-induced anaphylaxis in children. *J Allergy Clin Immunol* 2008; **122**: 133–8.
8. Ellis AK, Day JH. Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. *Ann Allergy Asthma Immunol* 2007; **98**: 64–9.
9. Kemp AS, Lockey RF, Simons FER. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy* 2008; **63**: 1061–70.
10. Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Epinephrine auto-injector use in adolescents at risk of anaphylaxis: a qualitative study in Scotland, UK. *Clin Exp Allergy* 2011; **41**: 869–77.
11. Simons FER, Lieberman PL, Read EJ, Edwards ES. Hazards of unintentional injection of epinephrine from autoinjectors: a systematic review. *Ann Allergy Asthma Immunol* 2009; **102**: 282–7.
12. Lippert WC, Wall EJ. Optimal intramuscular needle-penetration depth. *Pediatrics* 2008; **122**: 5e56–e563.
13. Muck AE, Bebartha VS, Borys DJ, Morgsan DL. Six years of epinephrine digital injections: absence of significant local or systemic side-effects. *Ann Emerg Med* 2010; **56**: 270–4.
14. Baris S, Saricoban HE, AK K, Ozdemir C. Papaverine chloride as a topical vasodilator in accidental injection of adrenaline into a digital finger. *Allergy* 2011; **66**: 1495–6.
15. Mrvos R, Anderson BD, Krenzelok EP. Accidental injection of epinephrine from an autoinjector: invasive treatment not always required. *Southern Med J* 2002; **905**: 318–20.
16. Arga M, Bakirtas A, Catal F, et al. Training of trainers on epinephrine autoinjector use. *Pediatr Allergy Immunol* 2011; **22**: 590–3.