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## Practical implications of issuing epinephrine prescriptions at primary health care facilities

### Praktyczne implikacje wystawienia pacjentowi recepty na adrenalinę w podstawowej opiece zdrowotnej

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#### Abstract

In their daily work, a primary care physician often meets patients with indications to issue a prescription for epinephrine for self-supply. However, they should not settle for writing a prescription, but also carry out full instructions as to the indications as well as the method of injection. The instruction should be carried out by a doctor or a nurse and be adapted to the specific medication that the patient will purchase. Attention should be paid not only to the patient, but also to all persons in the patient's environment who may be forced to administer epinephrine. The article discusses the mechanism of action of epinephrine, indications for its prescription and applicable contraindications. Attention was paid to the correct dosage of the drug, in particular – the need to prescribe at least two doses of the drug to the patient, so that the patient had at least two pieces of the medicine with him. Potential risks for the patient in the case of improper use are presented, for example a wrong route of administration. Differences between pre-filled syringes and auto-injectors are described. The preparations available on the Polish drug market (Adrenaline WZF and EpiPen) are presented. The work describes in detail how to use these devices, which allows a doctor or a nurse to prepare for the training of the use of a pre-filled syringe or an auto-injector. Attention is drawn to the application of training devices in order to instruct the use of the EpiPen.

**Keywords:** adrenaline, epinephrine, EpiPen, auto-injector, pre-filled syringe

#### Streszczenie

Lekarz podstawowej opieki zdrowotnej w swojej codziennej pracy ma często styczność z pacjentem ze wskazaniami do wystawienia recepty na adrenalinę (epinefrynę) do samodzielnej podaży. Nie powinien jednak ograniczyć się jedynie do wypisania druku receptowego; jego zadanie polega również na przeprowadzeniu pełnego instruktażu co do wskazań, a także co do metody wykonania iniekcji. Instruktaż powinien zostać przeprowadzony przez lekarza lub pielęgniarkę i być dostosowany do konkretnego preparatu, który będzie w posiadaniu pacjenta. Należy zwracać uwagę nie tylko na samego chorego, ale także na wszystkie osoby w jego otoczeniu, które mogą być zmuszone do podania adrenaliny. W niniejszym artykule omówiono mechanizm działania epinefryny, wskazania do jej przepisania i obowiązujące przeciwwskazania. Zwrócono uwagę na kwestie prawidłowego dawkowania leku, w szczególności zaś na konieczność przepisania pacjentowi co najmniej dwóch sztuk preparatów. Przedstawiono potencjalne zagrożenia dla chorego w sytuacji nieprawidłowego użycia, na przykład zastosowania niewłaściwej drogi podania leku. Opiszono różnice pomiędzy ampułkostrzykawkami i autowstrzykiwaczami, przedstawiono preparaty dostępne na rynku polskim (Adrenalina WZF oraz EpiPen). Szczegółowo opisano sposób użycia tych urządzeń, co umożliwi lekarzowi lub pielęgniarce przygotowanie się do prowadzenia szkolenia w zakresie użytkowania ampułkostrzykawkę bądź autowstrzykiwacza. Zwrócono też uwagę na wykorzystanie urządzeń treningowych do instruktażu korzystania z autowstrzykiwacza EpiPen.

**Słowa kluczowe:** adrenalina, epinefryna, EpiPen, autowstrzykiwacz, ampułkostrzykawka

## INTRODUCTION

A general practitioner at a primary health care facility often encounters patients, who should be advised to self-administer a life-saving medication in the case of an anaphylactic shock. Adrenaline (later referred to by its international name, epinephrine) is a prescription drug<sup>(1)</sup>, and it is the physician's responsibility to inform the patient about the indications for its application and administration. Due to numerous differences between the use of various products available on the market, a primary health care physician should indicate on the prescription which product the patient should buy or make another appointment with the patient after the purchase of the medication. During this visit, the patients would bring the product they bought, and the physician could show how to administer it properly. If the physician is preoccupied with other patients, the patient can go to a primary health care nurse, who can also instruct them on how to properly administer the medication.

### INDICATIONS FOR THE USE OF EPINEPHRINE

For more than 100 years, epinephrine has been a first-line treatment for anaphylactic shock<sup>(2)</sup>. Its efficacy is based on the knowledge and experience of generations of physicians, but to this day there has been no randomised study comparing epinephrine to a placebo, a lack of treatment, or to a similar drug. Considering the acknowledged and so-far uncontested efficacy of epinephrine in the cases of anaphylactic shock, such a study might be considered unethical<sup>(3)</sup>. The mechanism of epinephrine consists in it binding to adrenergic receptors, such as  $\alpha$ -1,  $\alpha$ -2,  $\beta$ -1,  $\beta$ -2, and  $\beta$ -3. Epinephrine acts on all 5 receptors, but to a different extent, depending on the dosage<sup>(2)</sup>. In the case of small doses, epinephrine affects mainly the  $\beta$ -1 and  $\beta$ -2 receptors, with moderate doses, it affects all receptors equally, and large doses influence mainly  $\alpha$ -receptors. The effect of epinephrine in the case of an anaphylactic shock is based on its effect on both  $\alpha$  and  $\beta$  receptors. The main benefits of administering epinephrine are:

- preventing hypovolemia due to the contraction of peripheral blood vessels, and avoiding fluid loss by decreasing the permeability of blood vessels;
- preventing respiratory failure by dilating bronchi and decreasing oedema of the upper respiratory tract;
- counteracting circulatory arrest by being a positive inotropic agent, which decreases the effect of inflammatory mediators<sup>(2,4)</sup>.

### INDICATIONS FOR THE PRESCRIPTION OF SELF-ADMINISTERED EPINEPHRINE

The three main indicators for prescribing self-administered epinephrine are<sup>(5)</sup>:

- a history of anaphylactic shocks;
- a food allergy (with the exception of allergic stomatitis) with coexisting uncontrolled, moderate, or severe chronic asthma;
- a mast cell disorder with a previously exacerbated allergic reaction to insect bites.

In some cases, a history of a severe allergic reaction AND one of the below factors, may be an additional indication for the prescription of epinephrine:

- Age – most cases of fatal anaphylactic shock caused by food allergies occur in teenagers and young adults. This group is especially at risk of being exposed to allergens when they are unsupervised by older adults.
- Specific allergens – allergies to hazelnuts, peanuts, and seafood may be fatal, even when those are consumed in very small amounts, which is not always possible to avoid. An allergy to insect bites without the occurrence of anaphylaxis is not a categoric indication for prescribing the medication, but combined with other risk factors, such as a place of residence and the time it takes for an ambulance to arrive, the patient's profession or coexisting conditions, it may be justified for the patient to carry epinephrine.
- Coexisting high-risk conditions – patients with asthma, cardiovascular conditions, or mastocytosis may need epinephrine as a preventative measure.
- Limited access to medical help – in the case of patients who live in areas where it takes a long time for medical rescue teams to arrive, it may also be justified to write out a prescription. This also applies to patients, who travel.

The following cases are not indications for prescribing epinephrine: a history of angioedema, general urticaria in children stung by an insect, topical reactions to insect bites, asthma without a history of anaphylaxis or exacerbated allergic reactions, allergic stomatitis, family history of anaphylaxis, or a reaction to easily avoidable agents<sup>(5)</sup>.

### CONTRAINDICATIONS

In the case of life-threatening anaphylaxis, there are no contraindications to administering epinephrine. The only condition is a correct diagnosis of a life-threatening condition, so administering the medication unnecessarily can be avoided. Pregnancy isn't a contraindication either, since the potential benefits are deemed to outweigh the risk of administering the medication.

The only relevant exception are patients with a diagnosed heart condition, for whom it is necessary to evaluate the potential risks and benefits resulting from the self-administration of epinephrine<sup>(4)</sup>.

### POSODOLOGY

The dosage of self-administered medication may be different from the dosage recommended for medical personnel,

so it is important to have in mind to whom epinephrine will be administered and who will be in charge of administering it. The dosage recommended for intramuscular administration by medical personnel is 0.3 to 0.6 mg for adults, and 0.01 mg/kg bw for children<sup>(4)</sup>. In Poland there are only two doses available:

- 300 µg (0.3 mg);
- 150 µg (0.15 mg).

The 300-µg dose is intended for patients who weigh more than 30 kg. The structure of auto-injectors allows only for the administration of the dose specified by the manufacturer. The structure of a pre-filled syringe, although similar to that of a regular syringe, does not allow to precisely reduce the pre-set dose, so it is not appropriate for patients who weigh less than 30 kg.

The 150-µg dose is intended for paediatric patients who weigh 15 to 30 kg. In the case of children who weigh less than 15 kg, the risk of an anaphylactic shock is usually smaller than in older children, but if necessary, a 150 µg EpiPen can be prescribed, if the physician is convinced that the benefits outweigh the risk of an epinephrine overdose. Due to the nature of anaphylaxis, the rate at which it develops, and the time for the medical help to arrive, it should be considered to advise the patient to carry two doses of epinephrine, and administering the second one after 5–15 minutes after injecting the first one, if the patient's condition does not improve or deteriorates. This problem may relate to patients with a large body mass in particular, for example, a child whose body mass is 28 kg and who carries a 150 µg self-injector, or an adult who weighs more than 80 kg and carries a 300-µg dose of epinephrine. There are cases indicating that not administering a second dose may have an adverse effect on the patients' health, so it is important to advise such patients to carry two doses<sup>(6)</sup>.

## RISKS FOR THE PATIENT

The medication may have adverse effects, and the patient should be informed about them beforehand. When administering epinephrine in the case of life-threatening anaphylaxis, the following symptoms may occur: the sensation of a racing heartbeat, feeling hot, sweating, a headache, difficulty breathing. Potential benefits usually heavily outweigh the consequences of adverse effects, though. A far greater risk is associated with an accidental administration of the drug, the wrong injection site, or administering the drug without indications. In such cases, the side effects may be more severe than usual.

Self-injectors are intended only for intramuscular administration. Intramuscular epinephrine injections are easy to perform, they act fast, and, most importantly, they are safer than intravenous injections, and are associated with a lower risk of arrhythmia, myocardial infarct and other cardiovascular complications<sup>(2)</sup>.

When prescribing epinephrine, especially in the form of pre-filled syringes, the patient should be advised that an

intravenous administration may be fatal. It should also be noted that subcutaneous administration of the drug has a slower and weaker effect than an intramuscular one, similarly to inhalation, so the best solution is to inject the medication into the muscle.

## INSTRUCTION FOR USE

The patient should be instructed on how to administer the epinephrine using a pre-filled syringe or auto-injector. Data from the USA suggest that patients may forget how to use certain auto-injectors even after 3 months<sup>(7)</sup>. On the other hand, many medical personnel employees were never trained to use such devices<sup>(8)</sup>. The patient should be instructed every time the device is changed, but also every time the epinephrine is prescribed<sup>(9)</sup>. Knowledge about various devices that are available and how to use them, will decrease the risk of administering the medication without indications, administering it accidentally or incorrectly.

At the moment, there are 5 products registered in Poland:

- Adrenalina WZF 300 µg/0.3 ml, pre-filled syringe;
- EpiPen Senior, 300 µg, auto-injector;
- EpiPen Jr., 150 µg, auto-injector;
- Anapen, 300 µg/0.3 ml, auto-injector;
- Anapen Junior, 150 µg/0.3 ml, auto-injector.

Since these products work very differently, the instructions for pre-filled syringes and auto-injectors will be presented separately. According to the available data, EpiPen is easier to administer compared to Anapen, and generates fewer application mistakes<sup>(10)</sup>. The availability of Anapen in Poland is very limited<sup>(11)</sup>, so its principles of use will not be explained in this article. The remaining products, even pre-filled syringes, like Adrenalina Aguettant, are intended for medical personnel only.

When instructing the patient, one should always point out the importance of calling an ambulance promptly and correctly, even if the patient's condition improves after the first dose. The patient should be warned about the consequences of the second phase of anaphylaxis, which may occur as late as several hours after the first incident.

Each time, it should be considered to instruct a larger group of people at once. Not only the patient but also the people accompanying the patient should be able to administer epinephrine in an emergency situation. In many cases, the patient may not be able to self-inject the medication and may therefore require assistance. In the case of paediatric patients, special attention should be given to the parents. The place where the child spends the rest of the time should also be taken into consideration, for example instructing teachers at school may be necessary as well.

## PRE-FILLED SYRINGES

The only epinephrine product available in Poland in the form of a pre-filled syringe is Adrenalina WZF, see Fig. 1. It resembles a regular syringe. It is filled with one



Fig. 1. Adrenalina WZF pre-filled syringe in a plastic blister.  
Source: private image

millilitre of solution containing one milligram of epinephrine, but the piston has a lock, which allows to administer only 0.3 ml of solution with a 300- $\mu$ g dose. Due to the structure of the lock, there is no possibility to administer a larger or smaller dose, and the pre-filled syringe cannot be re-used. Due to safety concerns, it is important to warn the patient against manipulating with the lock on the piston.

A pre-filled syringe is ready to be used, so there is no need to push out air from the needle – simply inject the medication. The medication can be administered only intramuscularly, and only into the anterolateral side of the thigh. Due to the structure and thickness of the needle, the injection site should be exposed. It is allowed to inject the medication through a thin layer of clothing. Make the injection when firmly holding the syringe in your hand and insert it into the thigh at a 90° angle. After inserting and removing the needle, massage the injection site for 10 seconds, which should increase the absorption rate<sup>(12)</sup>.

Adrenalina WZF expires after two years, but only if it is stored at cold temperature (2–8°C). Since the patient needs to carry the product with him/her, it can be stored at higher temperatures of up to 25°C, but it will expire within 6 months of being taken out of the fridge<sup>(13)</sup>.

An undeniable advantage of Adrenalina WZF is the fact that 50% of its cost is covered by health insurance. According to data concerning refunded medical products dated 1 January 2019, the retail price is 55.64 PLN, and in the case when it is covered by insurance – 27.82 PLN per one pre-filled syringe<sup>(14)</sup>. Both allergen-induced and idiopathic anaphylaxis are indications for receiving the refunded version of the drug.

## AUTO-INJECTORS

The main feature, which allows to distinguish auto-injectors from pre-filled syringes, is their image. An auto-injector resembles an insulin pen or a pen rather than a regular syringe. Auto-injectors for adult and paediatric patients look the same and vary only by dosage and colour – yellow is for adults, and green – for children. All devices are the same, and allow to inject only one, pre-set dose. In order to avoid accidental administration, they are equipped with safety locks on both ends. The product may be injected even through clothing, such as jeans or polyester, unless the clothing is too thick, which is significant especially in overweight patients, since the drug could be administered subcutaneously instead of intramuscularly<sup>(15)</sup>.



Fig. 2. EpiPen Senior auto-injector side A. Source: private image



Fig. 3. EpiPen Senior auto-injector side B. Source: private image

In order to use the EpiPen, shown in Figs. 2 and 3, grab it with your hand, unlock it by taking off the blue safety cover on the opposite end of the needle, insert into the thigh at a 90° angle, and keep it inserted for 5 seconds<sup>(16)</sup>. When the device is removed, the needle will retract into the orange cover, preventing accidental stabbing. After the injection, massage the injection site for 10 seconds. When instructing the patients, it is important to point out which side to inject with, since there have been cases of people trying to use the auto-injector, but inserting the needle into their thumbs instead<sup>(8)</sup>. The American manufacturer points out a mnemonic to easily remember the correct direction of the EpiPen, associating the colour blue with the sky, and orange with the thigh.

When using EpiPen Jr., it is important to immobilize the child's lower extremity during the injection, since there have been cases when the needle was broken<sup>(17)</sup>.

EpiPen and EpiPen Jr. can be stored at 25°C until the expiration date, which is 20 or 19 months, respectively. Please advise the patients to regularly check the condition of the medication through the viewing window<sup>(18,19)</sup>.

The manufacturer of EpiPen prepared a training device, which looks just like the real product, but doesn't contain the medication or a needle<sup>(20)</sup>. It can be used multiple times and allows to learn the correct hand-grip, how to unlocking the safety cover, and simulate the injection process. Due to safety concerns, the training device is labelled grey and has "trainer" or "training device" written on it in capitals.

## SUMMARY

A primary health care practitioner should not only possess knowledge about indications for prescribing self-administered epinephrine, but also be able to instruct potential users of auto-injectors and pre-filled syringes about indications for administration and the method of injection.

### Conflict of interest

The authors do not report any financial or personal connections with other people or organisations that could adversely affect the content of the publication and claim the right to this publication.

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