CLINICAL STUDY

Dilemmas regarding the proper route of adrenaline administration in anaphylaxis

Pijak MR, Gazdik F

1st Clinic of Internal Medicine, Faculty Hospital Ružinov, Bratislava, Slovakia. **bll@fmed.uniba.sk**

Abstract

The authors outline current practice regarding the pre-hospital use of adrenaline. They conclude that intramuscular adrenaline recommended in the current European guidelines may not be the only correct route of administration. Both intradermal and intravenous routes may be more appropriate in certain situations. The decision as to which route is the most appropriate in a particular situation will depend on several factors discussed in the article. Nevertheless, the early use of intramuscular adrenaline, particularly in pre-hospital or in the unmonitored setting, still warrants direct comparison with intravenous adrenaline to examine their relative efficacies compared with complication rates. Similarly, the benefits and risks of subcutaneous adrenaline in patients with milder reactions or increased cardiovascular risk warrant further investigation *(Tab. 3, Ref. 24)*.
Key words: proper route adrenaline administration, anaphylaxis.

The impulse for writing this article was the study by Gompels, et al (1) which highlights the confusion regarding the correct dose, concentration, and route of pre-hospital adrenaline (epinephrine) administration recommended in the treatment of anaphylaxis. Although the authors rightly point out that improved training in this area is required, further clarification of some points is warranted, especially with regard to the proper route of adrenaline administration. Indeed, in the past few years, there have been several debates on the indications for and optimal route of administrering adrenaline. Commentaries emphasise the need to re-evaluate current recommendations with regards to prevailing clinical conditions, clinical urgency, degree of circulatory compromise, availability of vascular access, and the level of care available (2, 3, 4).

Knowledge about using of adrenaline among senior house officers

In the beginning, it is worth mentioned the most important results of the Gompels, et al study. In this questionnaire-based survey, senior house officers, at the start of their accident and emergency post, were given an anonymous five case history questionnaire containing one case of true anaphylaxis and were asked to indicate the medication they would prescribe. The results showed that 45 % of the group decided to use intramuscular adrenaline and 42 % would administer adrenaline by the intravenous route. Moreover, out of the total of 78 respondents, only 5 % were able to indicate the correct route and dose of adrenaline according to current guidelines for the management of anaphylaxis in adults. Surprisingly, only a few respondents decided to use subcutaneous adrenaline. On the other hand, some respondents would administer intravenous adrenaline to patients who do not have potentially life threatening features.

Adrenaline undertreatment – overtreatment paradox

Based on these results, Gompels et al concluded that "there was a tendency to over-diagnose anaphylaxis, resulting in the over use of adrenaline." Although this cohort had not received formal teaching on anaphylaxis, these results are apparently alarming in view of the fact that over 100 000 epinephrine syringes have been prescribed throughout the UK for community use in the year 2001 (5) and that there was a 300 % increase of

1st Clinic of Internal Medicine, Faculty Hospital Ruzinov, Bratislava, Department of Immunology, Slovak Medical University, Slovakia

Address for correspodence: M.R. Pijak, MD, 1st Clinic of Internal Medicine, Faculty Hospital, Limbova 14, SK-833 05 Bratislava, Slovakia.
Phone: +421.2.59542439

Tab. 1. Resuscitation Council guidelines for anaphylactic reactions: treatment of adults by first medical responders (14).

Anaphylaxis should be considered:

When there is a history compatible with severe allergic reaction including respiratory difficulty and/or hypotension, especially with typical skin changes (urticaria and/or angioedema).

If the patient is assessed and there are STRIDOR, WHEEZE, and clinical signs of SHOCK present:

- Adrenaline should be administered as 0,5 ml 1/1000 solution (500 µg) intramuscularly, which may be repeated after five minutes.

Other treatments:

- Antihistamine (chlorpheniramine) 10–20 mg intramuscularly/or slow intravenously
- Hydrocortisone 100–500 mg intramuscularly/or slowly intravenously: for all severe or recurrent reactions and patients with asthma.
- If clinical manifestations of shock do not respond to drug treatment give 1–2 litres of intravenous fluid.

Other notes:

- An inhaled $beta_2$-agonist such as salbutamol may be used as an adjunctive measure if bronchospasm is severe and does not respond rapidly to other treatment.
- If profound shock is judged immediately life threatening give cardiopulmonary resuscitation/advanced life support as necessary. Consider slow intravenous adrenaline (epinephrine) 1:10 000 solution. This is hazardous and is recommended only for an experienced practitioner who can also obtain intravenous access without delay. Note the different strength of adrenaline (epinephrine) that may be required for intravenous use.
- If adults are treated with an Epipen, 300 µg will usually be sufficient. A second dose may be required.
- Half doses of adrenaline (epinephrine) may be safer for patients on amitriptyline or imipramine, intravenous salbutamol may be required for patients on a beta-blocker.
- A crystalloid may be safer than a colloid.

EpiPen prescriptions in Australia over the 1998–2002 years (6). Paradoxically, undertreatment is also a problem not mentioned by the authors. In fact, as pointed out by Ellis and Day (7) in their timely review, many cases of anaphylaxis are undertreated, with potentially life-threatening consequences. For illustration, an EpiPen device was only used in 29 % of cases in children with recurrent episodes of anaphylaxis (8) and only 7 % of children with peanut and tree nut allergy had a self-injection epinephrine device available (9).

The risk of death associated with anaphylaxis versus safety of adrenaline

There is a general agreement that the correct diagnosis and treatment of anaphylaxis can be life saving. However, no evidence exists that the more liberal community prescribing EpiPen has saved lives significantly. Furthermore, as pointed out by Unsworth (5) "Death following anaphylaxis is most feared but fortunately remains a very rare event, currently estimated at less than one case per year per million of the UK population (10)".

Likewise, a large child population based study of fatal and severe reactions to food from UK yielded only 0,006 fatal events per 100 000 children per year over the period 1990–2000 (11). It should be remembered that adrenaline is associated with some risk of cardiac arrhythmia, even when given in recommended doses (12). This danger is relatively high, because therapeutic and toxic doses are rather similar and the risk increases in patients with cardiovascular co-morbidity or who are taking medications with a potential of drug-drug interactions (13). It is therefore possible that the risk associated with improper administration of adrenaline or incorrect diagnosis might be higher than not administering adrenaline at all.

Pitfalls of current guidelines regarding intramuscular adrenaline

As Gomples et al correctly point out, the potential for misdiagnosis was recognised by the authors of Resuscitation Council guidelines (14). These British guidelines emphasize the importance of the first line treatment beeing safe, even in inexperienced hands. In this regard they unequivocally recommend non-intravenous adrenaline administration in initial pharmacologic management of anaphylaxis in a setting without monitoring and intensive care facilities. Furthermore, intramuscular administration is favoured because of faster absorption in comparison to subcutaneous route (Tab. 1). However, more disputable is the notion that adrenaline should be given only if the life threatening features such as hypotension and respiratory difficulty are present (14, 15). Accordingly, generalised urticaria, flushing, itching, and even angio-oedema, unless affecting the larynx, are not an indication for use of adrenaline. It is assumed that labelling of such benign reactions as anaphylaxis may render the subject vulnerable to being over-treated. However, such opinion neglects the fact that more than half of the patients may have mild symptoms for one hour or more before severe respiratory compromise develops (16). This may increase the risk of late administration of adrenaline which is generally associated with a poor outcome.

Tab. 2. Pre-hospital treatment protocol for anaphylaxis according to Massachusetts department of public health office of emergency medical services (22).

BASIC PROCEDURES

1) Activate ALS intercept if deemed necessary and available.
2) **BLS STANDING ORDERS**
   a) If patient presents in Severe Distress, as defined in Assessment Priorities, and if the patient age is between 5 and 65 years: administer epinephrine by auto-injection.
   b) A second injection may be administered, if available, in 5 minutes if necessary.

NOTE: Adult EPI-PENs® should be used in patients with a weight more than 30 kg (66 lbs).
Pediatric EPI-PENs® (EPI-PEN JR.® should be used in patients less than 30 kg (66 lbs).
NOTE: EMTs must contact Medical Control prior to administration of epinephrine by auto-injector when patient is under the age 5 or over the age 65.

3) If patient's BLOOD PRESSURE drops below 100 systolic: treat for shock.
4) Notify the receiving hospital.

INTERMEDIATE PROCEDURES

1) **INTERMEDIATE STANDING ORDERS**
   a) If patient presents with Severe Distress, as defined in Assessment Priorities, and if patient age is between 5 and 65 years: administer epinephrine by auto-injection.
   b) A second injection may be administered, if available, in 5 minutes if necessary.
2) Provide advanced airway management, if indicated.
3) Initiate IV Normal Saline (KVO) enroute to the hospital.
   If patient's BLOOD PRESSURE drops below 100 systolic: Administer a 250 ml bolus of IV Normal Saline, or titrate IV to patient's hemodynamic status

PARAMEDIC PROCEDURES

1) **ALS-P STANDING ORDERS**
   a) Provide advanced airway management (if indicated)
   b) Initiate IV Normal Saline (KVO) enroute to the hospital
   c) If patient's BLOOD PRESSURE drops below 100 systolic: Administer a 250 ml bolus of IV Normal Saline, or titrate IV to patient's hemodynamic status
   d) Mild Distress: monitor for signs of severe distress
   e) Severe Distress:
      - Epinephrine (1:1,000) 0.3 mg–0.5 mg SC; a second dose may be required
      - Large Bore IV normal saline, titrate to BLOOD PRESSURE >90
      - Diphenhydramine 25 mg–50 mg IV push or deep IM
      - Albuterol 0.5% (0.5 ml mixed with 3 ml of Normal Saline) via nebulizer

2) Contact **MEDICAL CONTROL**. The following may be ordered:
   a) Epinephrine (1:1,000) 0.3–0.5 mg SC
   b) Epinephrine (1:10,000) 0.1–0.5 mg IV Push
   c) Epinephrine Infusion 1–10 µg/min. Mix Epinephrine (1:1000) 1 mg in 250 ml Normal Saline (30 microdrops/minute = 2 µg/min)
   d) Albuterol 0.5% (0.5 ml mixed with 3 ml of Normal Saline) via nebulizer
   e) Diphenhydramine 25–50 mg IV Push or deep IM
   f) Dopamine infusion 2–20 µg/Kg minute (Rate determined by physician)

Rationale for the use of subcutaneous adrenaline

Indeed, there is now substantial clinical and experimental evidence available indicating that the delay of adrenaline administration is associated with both increased risk and decreased benefit (17, 18). Thus, it appears that underestimation of the milder reactions may be a double edge sword. One of the authors of this article, therefore suggested a compromise solution; in such situations, it would be reasonable to administer adrenaline subcutaneously instead of intramuscularly (2). The potential for harm following subcutaneous adrenaline administration is extremely small (19, 20), and its efficacy for prevention of anaphylaxis has been documented (21). Interestingly, according to American prehospital treatment protocols, non-medical persons or paramedical staff should administer adrenaline only subcutaneously (Tab. 2) (22). It is important to note that the use of adrenaline with milder symptoms will depend on the patient's history. A history of severe reaction is probably the most important criterion in the algorithm for identifying patients who may benefit from adrenaline. It should be noted however, that many anaphylactic reactions, especially those associated with insect stings, may occur without a documented prior exposure. Furthermore, a number of other factors may lower the threshold for when to administer adrenaline e.g., if the reaction is provoked by peanut, tree nuts,

Tab. 3. Proposed use of intravenous adrenaline in the treatment of anaphylaxis according to Brown et al (23).

1) Oxygen

- High flow oxygen (15 l/min) by facemask if SpO_2<92 or SBP<90 mmHg

2) Adrenaline infusion

- 1 mg in 100 ml (1:100 000, 10 ug/ml) intravenously by infusion pump
- Start at 30–100 ml/h (5–15 μg/min) according to reaction severity
- Titrate up or down according to response and side effects, aiming for lowest effective infusion rate. Tachycardia, tremor, and pallor in the setting of a normal or raised blood pressure are signs of adrenaline toxicity; consider a reduction in infusion rate
- Stop infusion 30 minutes after resolution of all symptoms and signs
- Continue observation for at least two hours after infusion ceasing (longer for severe or complicated reactions); discharge only if the patient remains symptom free

3) Normal saline rapid infusion

- 1000 ml (pressurised) infused over 1–3 minutes and repeat as necessary
- Give if hypotension is severe or is not responding promptly to adrenaline

4) Hypotension resistant to above measures

- Consider bolus adrenaline, glucagon (5–10 mg IV bolus followed by infusion) and noradrenaline infusion with invasive blood pressure monitoring and central venous access

seafood, a personal history of atopy and/or asthma, adolescence (especially late teens), failure to identify the responsible allergen in the meal and lack of access to emergency medical care.

Rationale for the use of intravenous adrenaline

Finally, it is important to mention the most controversial issue, the role of intravenous adrenaline in the treatment of anaphylaxis. According to current guidelines, this route of adrenaline administration should be reserved for patients with immediate life threatening profound shock where appropriate monitoring facilities exist. The reluctance to use intravenous adrenaline is mainly based on reports of rare cases of fatal adrenaline overdose (10). However, the opponents of the intravenous route ignore the fact that intravenous administration of adrenaline ensures rapid delivery to its site of action and avoids the problem of erratic and variable absorption. Notably, it is the time of maximum plasma adrenaline concentrations that affects the outcome. Recently, first prospective study significantly contributed to a reliable clinical evidence supporting the use of carefully titrated intravenous adrenaline with volume resuscitation for treatment of significant insect sting anaphylaxis (Tab. 3) (23). It is of interest that safety of intravenous adrenaline has also been documented in a small group of younger adults with acute life-threatening asthma (24). Thus, it seems, that the expert use of high dilution intravenous adrenaline in hospitals with appropriate monitoring may be the most optimal care for a patient with severe anaphylaxis. However, American guidelines admit intravenous route of adrenaline administration by experienced medical staff, even in pre-hospital setting (22).

Conclusion

To conclude, we would like to summarize that the intramuscular adrenaline recommended in current guidelines may not be the only correct route of administration. Both intradermal and intravenous routes may be more appropriate in certain situations. The decision which route is the most appropriate in a particular situation will depend on several factors discussed above. Nevertheless, the early use of intramuscular adrenaline, particularly in pre-hospital or in the unmonitored setting, still warrants direct comparison with intravenous adrenaline to examine their relative efficacies compared with complication rates. Similarly, the benefits and risks of subcutaneous adrenaline in patients with milder reactions or increased cardiovascular risk warrant further investigation.

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Received December 20, 2005.
Accepted January 5, 2006.