ISSN 1109-6888

Observational Study

Prehospital Management Of Near Fatal Anaphylaxis

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ABSTRACT

Prehospital management of near fatal anaphylaxis

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Anaphylaxis is a severe, potential life threatening allergic reaction, which is characterized by rapid onset and varied clinical manifestations involving in most of the cases the respiratory and cardiovascular systems and sometimes skin and mucosa. Twentysix patients (16♀ & 10♂) with a mean age of 59.7± 8.6yrs were included in this study. All patients were managed by Emergency Medical Services (EMS) of Thessaloniki. Triggers were medications in 25 patients and in 1 case food. Regarding medications, antibiotics were responsible for the vast majority of the cases (23 out of 25). On EMS arrival, 21 patients suffered hypotension, 2 intense bronchospasm, 1 pulmonary edema and 2 were in cardiac arrest (CA).

Moreover, 15 patients had generalized urticarial and 4 complained for abdominal pain. In 4 out of the 21 patients with hypotension, pulse was palpable only in the carotid artery and in the rest pulse was detectable in the radial artery but faint. One patient (the one with the pulmonary edema) had severe bradycardia (<30b/min). Of the 26 patients, 23 had a good level of consciousness (GCS: 15) and only 1 patient was in coma (GCS: 3). Initially, all patients received 0.5mg adrenaline IM. Thereafter, a peripheral IV line was established and fluids (LR), hydrocortisone and antihistamines were administered. Moreover, all of them received O_2 by mask at 10L/min. A second dose of 0.5mg adrenaline was administered in 8 patients, and 1 patient received an additional third dose. Adrenaline administration resulted in clinical improvement in a mean time of 6.1±4.2min. After clinical improvement, all patients were transferred into a hospital in good clinical condition. Cardiopulmonary resuscitation (CPR) according to the current European Resuscitation Council (ERC) guidelines was performed in the 2 CA victims and resuscitation efforts were terminated after 30min. In both CA victims, initial CA rhythm was asystole and did not change until the end of CPR. Early prehospital treatment of a severe allergic reaction by adrenaline administration can be lifesaving.

Keywords: Anaphylaxis, Allergy, Adrenaline, Antihistamine, Corticosteroids

INTRODUCTION

According to the World Health Organization (WHO) anaphylaxis is a severe, potential life threatening systemic hypersensitivity reaction, which is characterized by rapid onset and varied clinical manifestations, involving in most of the cases the respiratory and cardiovascular systems and sometimes skin and mucosa[1].

Several definitions are suggested in the literature. However, exact definition is not clinically important for anaphylaxis emergency management[2]. Anaphylaxis can be triggered by various factors, may have various clinical manifestations with different clinical severity and could lead to death[3].Despite the fact that most anaphylaxis definitions include involvement of several systems, only one system can be affected severely. Anaphylaxis incidence in Europe ranges between 1.5 to 7.9 per 100.000 persons per year[4]. It has been estimated that 0.3% of the total population could have an anaphylactic reaction during their life[5] and 1 out of the 3.000 hospitalized patients in USA[6]. Anaphylaxis prevalence has raised but fatal incidents remain constant or are even decreased[7]. Food, medications and bites are associated with anaphylactic reactions. Food is the most common trigger in children and medication in adults[8].

Death from anaphylaxis: According to registry studies data it seems that death from anaphylaxis is not common[9]. In one study from USA by Ma L et al[10], it has been presented that

anaphylaxis is fatal in 0.63 to 0.76/million population. Jerschow E et al analyzed 2.458 anaphylaxis deaths and concluded that medication was the primary trigger in 58.8% of the fatal anaphylactic reactions[11].

In fatal anaphylaxis, deaths usually occur shortly after exposure to an allergen. Especially, in cases of anaphylaxis associated with IV drug administration, death can occur within 5min after administration. There have been no reports of death after 6hrs of exposure to an allergen[12]. Elderly patients face an increased risk for fatal anaphylaxis independent of the trigger[11].

Clinical manifestations: Anaphylaxis has several clinical manifestations involving in most of the cases the respiratory and cardiovascular systems and sometimes skin and mucosa[13].Cutaneous symptoms may not be present or may not be obvious[14]. Symptoms which could lead to death involve the respiratory and cardiovascular system. Helbling A et al report an incidence rate of 7.9-9.6 cases per 100.000 population in Canton Bern inhabitants for anaphylaxis related cardiovascular compromise[15]. Those results are comparable with the ones of Yocum M et al, who in their study report an incidence rate of 8 cases per 100.000 population[16].

Symptoms: Anaphylaxis symptoms are not isolated only to one organ system, since anaphylaxis is a multisystem event. Symptoms may involve skin and/or mucosa. Skin symptoms are the most common ones and are present in 75% of the cases. On the contrary, hypotension is present only in 10% of the cases[17]. Signs and symptoms include:

Airway: Upper airway edema, laryngeal edema, hoarse voice, inspiratory stridor.

Breathing: Dyspnea, tachypnea, expiratory stridor, respiratory fatigue, cyanosis, confusion (due to hypoxemia), respiratory arrest.

Circulation: Tachycardia, hypotension, shock, fainting symptoms, collapse, altered mental status, unconsciousness, myocardial ischemia, and cardiac arrest.

Recognition: According to current guidelines anaphylaxis is considered to be present if:

1. Acute onset with skin and/or mucosa symptoms (erythema, generalized rash, urticaria, swollen lips, tongue swelling) with involvement of at least one of the following systems:
    - *Respiratory system:* Respiratory distress, dyspnea, bronchospasm, hypoxemia, PEF decrease
    - *Cardiovascular system:* Blood pressure decrease, symptoms of end organ dysfunction due to poor perfusion (hypotonia, collapse, syncope, incontinence)
2. Shortly after exposure to a possible allergen presentation of at least two of the following:
    - Skin and mucosa symptoms (rash, edema)

- Respiratory distress (dyspnea, bronchospasm, stridor, hypoxemia, PEF decrease)
- Blood pressure decrease or related symptoms (hypotonia, collapse, syncope, incontinence)
- Persistent gastrointestinal symptoms (abdominal pain, vomit)

3. Blood pressure decrease after exposure to an allergen which is known to be an allergy trigger for this specific patient

Clinical severity evaluation: The study of Brown S et al[17] analyzed 1.149 patients, who presented at the Emergency Department (ED) with hypersensitivity reactions. Authors suggested a classification method, based on clinical features on arrival:

- *Mild*: Only skin reactions
- *Moderate*: Respiratory, cardiovascular and gastrointestinal symptoms
- *Severe:* Hypotension, hypoxemia, neurological compromise

However, despite initial clinical manifestation, one can never be certain how quickly anaphylaxis will progress and how severe it will become.

Medication Treatment: Anaphylaxis is a medical emergency and should be recognized and managed immediately. Despite the fact that epinephrine is the drug of choice for anaphylaxis management, its routine use still remains suboptimal[8,18,19]. Administration of other drugs should be discussed only after epinephrine has been used.

Epinephrine is a natural catecholamine acting on a and b adrenergic receptors. Through its action on a1 receptors, epinephrine induces vasoconstriction, increases the arterial blood pressure and decreases mucosa swelling. Through its b1 action, it increases myocardial contractility, and enhances coronary perfusion. Finally, through its b2 action, it induces bronchodilation. Within a few min, epinephrine reverses the effects of mediators on end organs, stabilizes mast cells and prevents further degranulation and mediator release.

Traditionally, *corticosteroids* and *antihistamines* have been used for the treatment of anaphylaxis. However, there are only limited data supporting their efficacy on anaphylaxis management[20,21]. Antihistamines can have a positive effect on symptoms, which are neither severe nor life threatening such as itching, which are mediated through histamine receptors. Moreover, there are not sufficient scientific data supporting that corticosteroids prevent biphasic anaphylactic reactions[22,23].

Recommended epinephrine dose for intramuscular (IM) administration is 0.01mg/Kg (max dose 0.5mg), using concentration of 1:1.000, given IM into the anterolateral thigh. This dose may be repeated every 5min if symptoms persist. Intramuscular as opposed to intravenous administration is safe, well tolerated by patients and does not cause any harmful ef-

fects[24,25]. Therefore, IV administration should be used only by expert and well trained health care professionals. Additional use of nebulized epinephrine may be helpful for the management of upper airway mucosa edema[26].

Additional treatment: Based on available data it seems that anaphylactic shock is caused by venous return decrease (due to vasoparalysis), fluid extravasation and mediators effects on cardiac function[27].

Adequate *fluid administration* corrects hypovolemia and makes epinephrine administration even more effective. Aggressive fluid administration is recommended in cases of treatment resistant anaphylaxis[8,28,29]. Oxygen administration is considered as standard routine therapy in every patient with anaphylaxis.

Emergency Medical Services (EMS) in Greece: Prehospital emergency medical care in Greece is provided by the National Centre for Emergency Care (Ethniko Kentro Amesis Boitheias-EKAB) which was established in 1987[30]. The national emergency call number is 166/112. EKAB is a two tiered EMS consisting of two types of ambulances, Basic Ambulances (BAs) and Mobile Intensive Care Units (MICUs). BAs are staffed with Emergency Medical Technicians (EMTs) and appropriately equipped for oxygen administration, basic airway management, trauma stabilization, IV line placement and with AED. According to local protocols, EMTs can administer drugs only after telephone communication with the physician in the Dispatch Center (DC). MICUs are staffed with a physician and EMTs and equipped with advance life support drugs and manual defibrillator. In big cities EMS motorbikes are also available.

MATERIALS AND METHODS

Twenty six patients, who suffered from a severe anaphylactic reaction and were managed by EKAB of Thessaloniki, were included in this study. In all cases, family members of the patients called the EKAB DC, due to clinical manifestations, which occurred after food or drug administration and were suggestive of anaphylaxis. DC staff was able to collect necessary information in all cases and dispatched a BA and a MICU simultaneously.

Anaphylaxis was managed according to the current guidelines. IM administration of 0.5mg epinephrine was followed by IV line placement and fluid administration. Epinephrine administration was repeated after 5min when symptoms persisted. Moreover, after epinephrine administration all patients received IV 250mg hydrocortisone and 4mg dimetindene. CPR was performed in CA victims according to ERC current guidelines. All patients were transferred to the ED for further management and hospitalization.

RESULTS

Patient demographic data and response times of BAs and MICUs are depicted on Table 1.

Number of patients (n)	26
Gender (m/f)	10 /16
Age (yrs)	59.7±8.6
EMS Response Time • BAs • MICUs	 7.3±3.1 9.1±3.6

Values are mean±SD, m: male, f: female, BAs: Basic Ambulances, MICUs: Mobile, Intensive Care Units

Table 1. Demographic data and EMS response times

Triggers of anaphylaxis are depicted on Table 2.

Medications	n=25
• Antibiotics (cephalosporin) • Mefenamic acid	n=23 n=2
Food	n=1

n:number of patients

Table 2: Anaphylaxis triggers

In 23 cases drugs were administered per os and in the two CA victims IM.

On EMS arrival, 21 patients suffered hypotension (SAP<90mmHg), 2 intense brochospasm, 1 pulmonary edema and 2 were in cardiac arrest (CA). In 4 out of the 21 patients with hypotension, pulse was palpable only in the carotid artery and in the rest pulse was detectable in the radial artery but faint. One patient (the one with the pulmonary edema) had severe bradycardia (<30b/min).

Moreover, 15 patients had generalized urticarial and 4 complained for abdominal pain. Of the 26 patients, 23 had a good level of consciousness (GCS: 15) and only 1 patient was in coma (GCS: 3). After initial treatment, there was clinical improvement in 24 patients all of whom were able to walk without feeling faint and were transferred to the ED for further management and hospitalization. In both CA victims, initial CA rhythm was asystole and did not change until the end of CPR, which was terminated after 30min.

DISCUSSION

All patients included in our study were managed in the prehospital setting by EMTs and a physician of EKAB Thessaloniki, since BAs and MICUs were simultaneously dispatched in all cases. It should be clarified that only patients with a severe anaphylactic reaction were included in the study and patients with mild symptoms were managed by EMTs, only without dispatching a physician and thereafter they were transferred to the ED by BAs. According to current practice, MICUs are dispatched only for critically ill patients. MICUs are dispatched either simultaneously along with BAs when there is already information suggesting a critically ill patient case or after arrival of BAs on scene of the incidence and severity assessment by EMTs. In all cases information was clear and clinical condition was decided to be severe by DC.

Recognition of anaphylaxis is relatively easy when there is acute onset after exposure to an

allergen.Shorter response time for BAs is only reasonable since a higher number of BAs compared to MICUs are available and moreover because BAs are located at different spots all over the city.

For the vast majority of the cases medications were recognized as anaphylaxis triggers. Antibiotics and non-steroids are the most common drugs associated with anaphylaxis and medications in general are the main cause for anaphylactic reactions in adults[31,32].

On EKAB arrival, most patients suffered hypotension. Regarding skin involvement not all patients had skin reactions. It is known that anaphylactic symptoms can range from mild to anaphylactic shock and absence of skin reactions usually delays diagnosis[33].

In all patients, 0.5mg epinephrine was administered IM before any other intervention. Epinephrine is drug of choice for anaphylaxis treatment[29]. According to current and previous guidelines, IM epinephrine administration is strongly recommended. Evidence is not strong since it is difficult to conduct randomized studies for life threatening clinical conditions[34,35]. However, evidence in favor of epinephrine administration is stronger compared to the corresponding one regarding corticosteroids and antihistamines[33]. Recommended route and site of administration is IM and on the anterolateral thigh[24,25]. Intramuscular as opposed to intravenous administration is not associated with any harmful effects[24,25]. Nebulized epinephrine might be helpful in patients with laryngeal or pharyngeal edema but systemic absorption is low and therefore this route of administration is not effective alone[14,19].

A second dose of 0.5mg epinephrine was administered in 8 patients. According to current and previous guidelines, epinephrine administration should be repeated if symptoms persist after 5-15min[1,36,27]. Patel N et al conducted a meta-analysis and concluded that 1 out of 10 patients needs at least one additional epinephrine dose[37]. Several risk factors associated with the need for additional epinephrine administration have been identified in the literature[38-40].

Epinephrine was administered immediately after MICU arrival on scene. According to local protocols EMTs in Greece are not allowed to administer drugs without physician consultation. Epinephrine should be administered immediately after onset of symptoms[8]. Despite the fact that there isn't any strong evidence regarding optimal time of epinephrine administration, literature studies report that early administration is associated with better outcomes[28] and a lower percentage of biphasic reactions[34].

Immediately after epinephrine administration, all patients received cortisone and antihistamines (250mg hydrocortisone and 4mg dimetindene). Corticosteroids and antihistamines are considered second line treatment for anaphylaxis[34]. Antihistamines play a limited role in anaphylaxis treatment and they might

reduce skin reactions[41]. Their routine administration remains controversial[33,42,43].

All patients received crystalloids, namely LR.

Anaphylaxis causes vasodilatation which impairs cardiac function. Therefore, isolated epinephrine administration without volume restoration might not be effective[27,44-46].

On EKAB arrival, 2 patients were in CA. Anaphylaxis related death is estimated to be lower than 1%[8]. Risk factors for fatal anaphylaxis are comorbidities and late epinephrine administration. In most of the cases death in anaphylaxis occurs before epinephrine administration. In our study, CA occurred in patients, who had received antibiotics IM and before EKAB arrival on scene. Fatal anaphylactic reactions are associated with medications and our results are in accordance with most literature studies[31,32]. In such cases death usually occurs quickly after exposure to the allergen[8,12].

Time of symptoms onset is related to route of drug administration[12,47]. Quick onset resulted in death before appropriate treatment.

Despite the fact that fatal anaphylaxis is rare even if epinephrine is not administered and in most of the cases symptoms subdue without any intervention, it is important that anaphylaxis is treated as a potential life threatening condition, since it's difficult to predict its clinical severity[1,34].

Performing CPR on a CA victim due to anaphylaxis does not differ compared to other CA circumstances[48]. However, it remains an issue of scientific debate whether chest compressions are effective in the vasodilated CA victims[49-51]. Extracorporeal Membrane Oxygenation (ECMO) use might be helpful but there isn't yet any relevant documentation in favor of this. According to International Liaison Committee on Resuscitation (ILCOR) recommendations, ECMO can be applied in selected CA victims after anaphylaxis, when CA is resistant to standard CPR[52-54].

Limitations of the study

This study only included anaphylaxis cases where MICU dispatch was decided. Therefore, it does not represent the total number of anaphylactic reactions calls received by EKAB DC. Since there is no data registry for anaphylactic reactions, we don't know the exact prevalence and severity grade of anaphylaxis in the region of Thessaloniki.

CONCLUSION

Anaphylactic reactions could potentially be life threatening. Epinephrine is first line treatment of severe anaphylaxis and its early administration can be lifesaving. Therefore, epinephrine administration should precede any other intervention and other drugs administration is not allowed to delay epinephrine administration.

Addittional materials: No

Acknowledgements: Not applicable

Authors' contributions: FB drafted the paper and is the lead author. AA contributed to planning and the critical revision of the paper.

FK contributed to planning and the critical revision of the paper. PA contributed to planning and the critical revision of the paper. ChE contributed to planning and the critical revision of the paper. OV contributed to planning and the critical revision of the paper. KK contributed to planning and the critical revision of the paper. GV contributed to planning and the critical revision of the paper. All authors read and approved the fnal manuscript.

Funding: Not applicable.

Availability of supporting data: The datasets analyzed during the current article are available from the corresponding author on reasonable request.

Ethical approval and consent to participate: Ethics committee approval required.

Competing interests:

The authors declare that they have no competing interests.

Received: June 2023, Accepted: June 2023, Published: June 2023

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Citation: Fyntanidou B, Amaniti A, Fortounis K, Papadopoulos A, Chatsiou E, Ourailoglou V, Kotzampassi K, Grosomanidis V. Prehospital management of near fatal anaphylaxis. *Greek e j Perioper Med. 2023;22 (b): 16-29.*