

Delayed Epinephrine Administration and Biphasic Anaphylaxis: A Case Report

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Abstract: Introduction: Anaphylaxis is a potentially life-threatening, acute systemic hypersensitivity reaction, which usually represents an Ig-E mediated allergy. Bee sting may induce anaphylaxis reaction, with near fatal and fatal outcomes. Epinephrine, the essential first line in the treatment of anaphylaxis, is some of the time not administered. Delayed epinephrine administration played a role as prognostic factor in anaphylaxis that can contribute to the occurrence of biphasic reaction. Here we report a case of delayed epinephrine administration and biphasic anaphylaxis. Case Report: Female, 26 year-old, came to hospital with complain of itchiness, reddish, swelling locally and numb in the left hand, worsen palpitation and tachypnea 10 hours after stung by bee. She has no history of allergic disease. She was given epinephrine 0.3 ml intramuscularly, with other adjuvant therapy. The symptoms were getting better after 10 minutes administration of epinephrine. Discussion: Symptoms in the patient met the Sampson criteria for anaphylaxis and is classified into moderate reaction based on Brown criteria. In this case, there was a delayed epinephrine administration which may be related to the development of biphasic anaphylaxis. Conclusion: Delayed epinephrine administration is associated with increase morbidity and mortality from anaphylaxis.

Keywords: epinephrine, anaphylaxis, biphasic reaction, bee sting

1. Introduction

Anaphylaxis reaction is an acute systemic hypersensitivity reaction caused by release of mediators from mast cells and basophils, which involve more than one organ systems: skin, mucosa, respiration, cardiovascular, and gastrointestinal system and is potentially life-threatening.[1] Incidence of anaphylaxis can be vary from 6.7-56 per 100.000 person-years, with fatality rate around 0.65% of cases.[2]

Anaphylaxis usually represents an immunological reaction, most often an immunoglobulin-E mediated allergy. Food and drug allergy, as well as insect sting are the top three causes of anaphylaxis worldwide.[3],[4] Systemic reaction induced by bee sting may shows only urticarial as the only clinical manifestation to a full blown anaphylaxis with near fatal or fatal outcomes.[5]

Anaphylaxis can show different manifestation in the same person, even when triggered by the same allergen. The inconsistency of anaphylaxis signs and symptoms sometimes make it treated inadequately. Intramuscular epinephrine is the first emergency medication indicated in anaphylaxis treatment.[6]

Some of the time, epinephrine is not administered even when anaphylaxis was correctly diagnosed. [7], [8] Antihistamines and corticosteroids are often the first medications administered to patients presenting with anaphylaxis. It is concerning given that most cases reported deaths from anaphylaxis have been associated with delayed administration of epinephrine.[6],[9]

Delayed administration of epinephrine is also believed to be one of risk factors the occurrence of biphasic anaphylaxis. Biphasic anaphylaxis is one of the morbid sequelae of an

anaphylactic reaction, which is still poorly understood and said to be occur in 1 in every 5 cases of anaphylaxis. [10], [11] It is important to note that in the setting of anaphylaxis, there is no absolute contraindication of epinephrine administration.[6]

2. Case Report

The patient was 26 years old female, 55 kg weight. The patient arrived at emergency department at 00.58 am with history of stung by bee at 03.00 pm the day before. Before going to hospital, she only feels itchiness, reddish, swelling locally and numb in the left hand, and a little palpitation. At the time she had not experience any dizziness, breathless or chest pain. The patient then bought herself some medicine without prior consultation to the doctor, but she feels worsen by hours and decided to go to emergency department. She did not remember the name of drug she bought. On arrival to the emergency department, she was tachypnea, feels worsen palpitation, itchiness and local swelling of the left hand.

She had a history of bee sting previously, with no history of drug and food allergy. She had no prior atopic history. She works in a fruit shop, and for the last 2 weeks, she had been stung by bee around 5 times. Only this time she feels severe symptoms and decided to go to the hospital to ask for help.

Blood pressure was 130/90 mmHg, heart rate rose to 145 beats per minute, respiratory rate was 24 per minutes with oxygen saturation 97%. We did not find any gastrointestinal symptoms or facial angioedema in her eyes at the time. The lungs bilaterally presented vesicular, without wheezing and rhonchi. She was alert and conscious during her arrival in emergency department. Epinephrine with dose 0.3 ml intramuscularly, oxygen 3 liter per minutes via nasal cannula and IV line administration was given to the patient.

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Methylprednisolone was given intravenously at first with dose 125mg then followed by dose 62.5 mg every 12 hours. Loratadine 10 mg orally was also given to the patient every 12 hours. After 10 minutes, shortness of breath and the tachycardia become better. Her vital signs were stable with a blood pressure of 120/80 mmHg, heart rate decrease to 88 beats per minutes, respiratory rate improve into normal rate 20 times per minute, with oxygen saturation 99-100% via pulse oximetry. She then transferred to intensive care for further evaluation. Her consciousness was clear, breathing was smooth, she saved successfully.

Preliminary blood investigation taken on arrival to the emergency department showed mild leukocytosis ($12.45 \times 10^3/\mu\text{L}$), eosinophilia (4.2%) and elevated total Ig-E (122 IU/mL). Electrocardiogram showed sinus tachycardia (HR 143 bpm).

3. Discussion

Anaphylaxis is uncommon but not rare. The incidence of anaphylaxis in adults is suggested to be 30 per 100.000 person year and the prevalence of life-threatening anaphylaxis has been estimated at 5-15 per 100.000.4,8 The onset of anaphylaxis is sudden and without warning, and often occurs outside of a medical setting, for example after consuming certain food or stung by insect.12 Foods, insect venoms/stings and medications are the most common provoking factors for anaphylaxis.[4],[12]

The diagnosis of anaphylaxis can be established based on *Sampson* criteria: (1) acute onset (in minutes or few hours) with involvement of skin and mucosa (generalized pruritus, flushing, swollen of lips, tongue and ovule) or both, along with respiratory symptoms (difficulty in breathing, wheezing, stridor, hypoxemia) or decrease of blood pressure, collapse, syncope, incontinencia; (2) two or more following

symptoms which occur immediately after allergen exposure- skin and mucosa involvement, respiratory symptoms, decrease of blood pressure, collapse, syncope, incontinencia, or gastrointestinal symptoms; (3) blood pressure <90 mmHg immediately after exposure or decreased more than 30% from initial blood pressure.[13] Symptoms found in the patient met *Sampson* criteria for anaphylaxis, such as involvement of skin (itchiness or pruritus, swelling of left hand) and difficulty of breathing which happen in acute phase.

The severity of anaphylaxis varies from one episode to episode even with an identical stimulus in the same patient and can be classified into mild, moderate and severe based on *Brown SGA*. [12],[14] Mild if only involve the skin and mucosa, moderate if involve respiratory, cardiovascular, and/or gastrointestinal system, and severe reaction if causing hypoxia, hypotension, and/or CNS disorders.[14] This case is classified into moderate reaction because it only involved skin and respiratory system, without collapse or loss of consciousness.

Must be noted that the severity of initial phase of an anaphylactic reaction is not predictive of either biphasic or protracted anaphylaxis, although failure to give an adequate dose of epinephrine initially may be associated with increase in the occurrence of biphasic anaphylaxis.[12]

Most anaphylactic reactions are Ig-E mediated and test to demonstrate Ig-E antibody should be performed.[3] Increased of total Ig-E value was found in this case.

The patient was administered epinephrine 0.3 mL intramuscularly, methylprednisolone 125mg intravenously, loratadine 10mg orally, and oxygenation in emergency department. The symptoms was improve 10 minutes after epinephrine injection. Adrenaline (epinephrine)

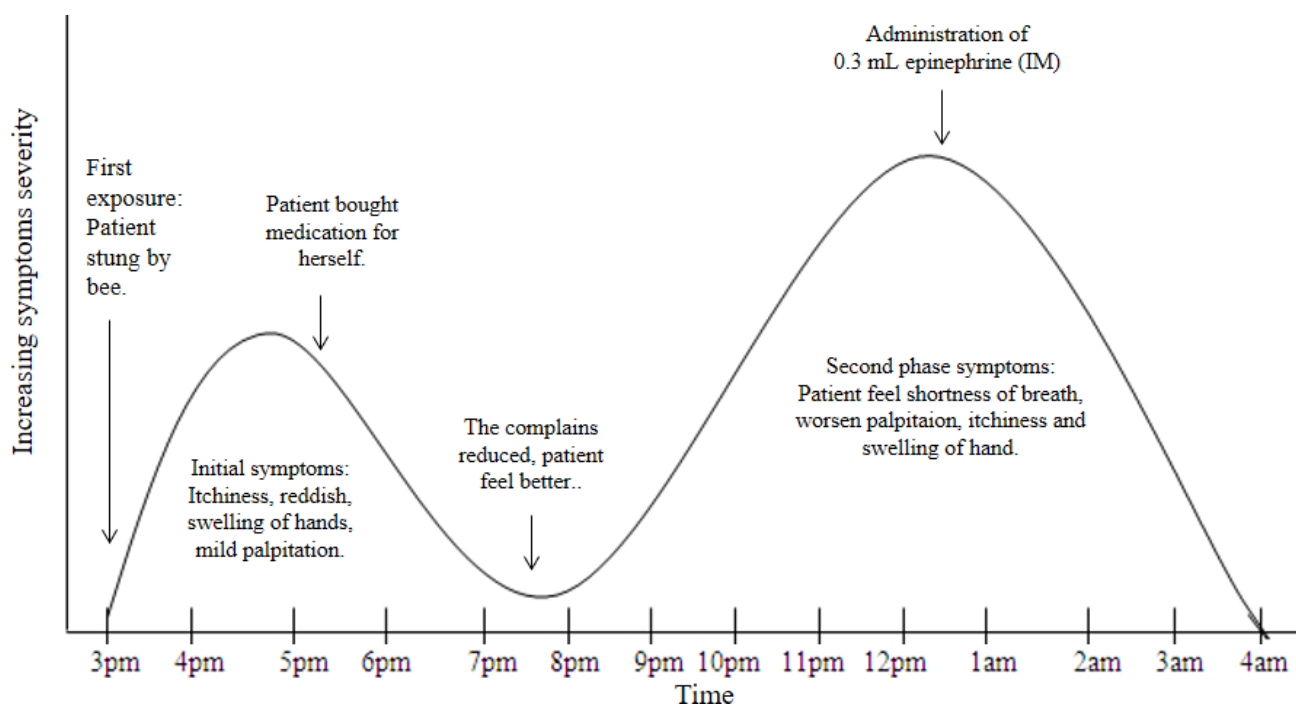


Figure 1: Case chronology time lapse

is the most important drug in the acute therapy of anaphylaxis and should be given as soon as the condition is recognized. Volume support, nebulized bronchodilators, antihistamines and corticosteroids should be regarded as adjuvant to adrenaline. Intramuscular 1: 1000 (1 mg/mL) adrenaline at a dose of 0.005-0.01mg/kg (0.005-0.01 mL/kg) body weight up a maximum dose of 0.5 mg (0.5 mL) injected intramuscularly into the lateral thigh (*vastus lateralis*), and can be repeated after 3-5 minutes. [3], [4], [8], [15]

In this case, unfortunately, there was a delayed epinephrine administration caused by delayed hospital arrival of the patient. Although epinephrine is the only effective treatment to prevent progression of an anaphylaxis, its underuse has been reported in many studies. This is especially troubling given the fact that fatal anaphylaxis has been associated with delayed administration of epinephrine.[6],[9]

Epinephrine functionally antagonizes all of the important pathomechanism of anaphylaxis through the activation of α - and β -adrenergic receptors, which lead to vasoconstriction, vascular permeability reduction, bronchodilatation, inhibit release of inflammatory mediators, reduction of edema and positive inotropic in the heart. There is clear evidence that intramuscular administration of epinephrine in the anterolateral thigh achieves faster and higher peak plasma concentrations compared with administration via subcutaneous route.[8],[9]. Intramuscular route also has lower risk for severe cardiac side effects compared to intravenous administration.[3],[6]

There is no absolute contraindication for adrenaline in the case of life-threatening anaphylaxis. A chart review study conducted in USA shows early treatment of anaphylaxis with epinephrine (received epinephrine before arrival to the emergency department) was associated with significantly lower risk of hospitalization (OR 0.25; 95% CI, 0-12-0.49).[3],[6],[8] A retrospective cohort study of 761 adult patients with anaphylaxis also show there was a reduced risk of hospital occurrence hypotension when epinephrine given to anaphylaxis patients with stable hemodynamic (OR 0.254; 95% CI, 0.091-0.706). Adverse events of epinephrine were rare when it given intramuscularly.[16]

Fatalities during witnessed anaphylaxis, which mostly occur outside medical setting, usually result from delayed epinephrine administration. Delayed hospital arrival or delayed recognition for treatment, which result in delayed administration of epinephrine has been shown to be associated with increased risk of hospitalization, severity of reactions and fatalities.[2],[12] In a retrospective review of 6 fatal and 7 nonfatal episodes of anaphylaxis, all subjects who survive had received epinephrine before or within 5 minutes of developing severe respiratory symptoms. None of the subjects with fatal attacks received epinephrine before the onset of severe respiratory symptoms.[13]

This patient was hospitalized for 2 days. An observation period of 8 hours is sufficient for most cases, but since reaction can occur as long as 72 hours after resolution of the primary event, some authors have recommended a 24 hours

waiting period.[10] Monitoring of patients for 24 hours or more after apparent recovery from the initial phase may be necessary in more severe cases because life-threatening manifestations of anaphylaxis may recur. Further allergen exposure should be stopped if possible.[3],[12]

The patient was already feels better before seeking for medical help, but several hours later the complaint reappearing and worsen. The patient even start feeling shortness of breath. Some patient with anaphylaxis may show a biphasic reaction. Biphasic reaction is the second episode of anaphylaxis that follows the brief resolution of symptoms period after the initial anaphylaxis reaction without further exposure to the triggering factors.[11]

The incidence of biphasic anaphylaxis as described is highly variable, ranging from 1-20% of episodes.[10] The severity of the first reaction, the time of onset after administration of antigen before the occurrence of symptoms of the primary response, the presence of hypotension or laryngeal edema during the primary reaction, history of biphasic reaction, delayed in administration of epinephrine and too small dose of epinephrine given in the primary reaction have all been mentioned in various studies as risk factor of biphasic anaphylaxis.[10]

A cohort study held in Thailand detected 6.25% of anaphylaxis patients develop biphasic reaction and among the patients who develop biphasic reaction, a significantly longer time from onset of symptoms to the administration of epinephrine was detected. These findings support the early administration of epinephrine to prevent late-phase anaphylaxis. The time from initial event to onset of second anaphylaxis reaction ranged from 2 to 13 hours, with a mean of 7.84 hours.[2]

The clinical severity of the second phase of biphasic anaphylaxis does not necessarily resemble the first. Even are still yet to be proven, there are few possible risk factors that suggested may increase the likelihood of biphasic anaphylaxis, such as severe initial symptoms, delayed administration of adrenaline during the initial treatment, a longer time for the initial reaction to resolve, delayed onset of initial symptoms after exposure to the antigen and exposure to allergens in the form of oral ingestion.[10],[11]

Prognosis to anaphylaxis reaction can be vary among the people, but older age, history of atopy, history of cardiovascular disease, chronic obstructive pulmonary disease or asthma, preceding intake of β -adrenoceptor antagonists, ACE inhibitors, and non-steroidal anti-inflammatory drugs (NSAIDs), electrolytes or acid-base imbalance, and delayed epinephrine administration may lead to deterioration of anaphylaxis symptoms.[1],[3],[4] The only factor that worsen the prognosis in this case was the delayed epinephrine administration, which may also related to the occurrence of biphasic anaphylaxis. The outcome of severe anaphylaxis is fatal in 0.65-2% of cases, causing 1-3 deaths per million people annually.[8]

Optimizing prevention is crucial because future anaphylaxis may be fatal despite appropriate management. Strategies to

avoid the precipitants should be customized. In case of bee sting hypersensitivity, patients should be advised to avoid consuming sweet foods or drinks out of doors as these attract bees and wasps. Allergen immunotherapy with appropriate insect venom is recommended for patients with anaphylactic reactions caused by insect stings. This may reduce risk of anaphylaxis from repeated stings and is associated with an improved patient's quality of life.[4],[8]

All patients who are at risk for future anaphylaxis need to be trained to recognize early warning symptoms and should carry at least one epinephrine syringe, know how and when to administer it. The possibility of biphasic anaphylaxis as well as a late phase-reaction has to be kept in mind.[3]

4. Conclusion

Bee stings can lead to clinical symptoms in the form of local and systemic reaction. Anaphylaxis reaction caused by bee stings can be proven by increase of total Ig-E and can be fatal even on the first reaction. Even in patients without early symptoms, long-term monitoring is essential to avoid morbidities and more severe outcomes including biphasic reaction and death.

Delayed epinephrine administration is associated with increase morbidity and mortality from anaphylaxis. This risk can be minimized by recognizing the variable signs and symptoms of anaphylaxis and treating promptly with intramuscular epinephrine. Early administration of epinephrine may also have a role in prevention of biphasic reaction.

5. Other Recommendation

The referral to an allergist specialist is necessary for further diagnostic work-up, to identify or confirm the cause, to educate regarding appropriate avoidance strategies, to help in drafting an emergency action plan and to advise whether immunotherapy is appropriate.

Further research about biphasic anaphylaxis is needed to provide a better understanding about the prevention of biphasic anaphylaxis, identification of patients who is at risk for biphasic reaction, observation strategies in anaphylaxis patients and patient education and preparation for management of potential biphasic reaction.

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