

Update on epinephrine for the treatment of anaphylaxis

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Purpose of review

Epinephrine is the treatment of choice for anaphylaxis – a life-threatening and potentially fatal event. The purpose of this review is to highlight recent publications relevant to the management of anaphylaxis and identify potential barriers which prevent or delay appropriate administration of epinephrine.

Recent findings

Experts have moved towards a consensus on how to define anaphylaxis, which has a variable clinical presentation. A clear definition, across specialties, is necessary for more accurate determinations of prevalence, diagnosis and management. Epinephrine injected intramuscularly is the treatment of choice, but there remain gaps in physician knowledge despite increases in hospitalization rates for anaphylaxis. Epinephrine is also underused by parents, day-care centers and schools. Barriers to access for treatment exist in lower socioeconomic groups. Women appear to be at risk for suboptimal treatment when autoinjectors are used. Given these issues, other routes of administration of epinephrine have been explored. Epinephrine delivered via a sublingual route has been successful in animal studies.

Summary

Epinephrine is the primary therapy for anaphylaxis, yet studies show that it is underutilized. By addressing the contributory factors that have been identified, acute and long-term care of individuals with this potentially life-threatening disorder can be optimized.

Keywords

anaphylaxis, autoinjectors, epinephrine

Introduction

Epinephrine is the treatment of choice for anaphylaxis. Delays in administration can result in severe respiratory compromise, cardiovascular collapse or fatality. This review highlights publications from January 2005 through September 2006 in anaphylaxis, focusing specifically on treatment with epinephrine. Important developments during this period include advances in establishing a consensus definition of anaphylaxis, which is essential for improving treatment guidelines. Inadequacies in the knowledge base of both physicians and patients have been illuminated, which are valuable for directing future educational efforts. Shortcomings in availability and delivery of epinephrine have also been identified. Finally, preparedness of schools in appropriate treatment of anaphylaxis has been explored, particularly for children at risk.

Definition of anaphylaxis

The lack of a universal agreement on the definition of anaphylaxis or the criteria for diagnosis has been a limiting factor for research into epidemiology and pathophysiology. This has led to inconsistency among medical personnel in diagnosis and management. In 2004 and 2005, however, the National Institute of Allergy and Infectious Diseases convened an expert panel to establish a definition of and clinical criteria for anaphylaxis [1,2^{••}]. The panel proposed a brief definition of anaphylaxis useful for both medical and lay populations: 'Anaphylaxis is a serious allergy reaction that is rapid in onset and may cause death' ([2^{••}], p. 392). Moreover, specific clinical criteria for diagnosing anaphylaxis were put forward with the intent to capture more than 95% of cases of anaphylaxis (Table 1). An updated practice parameter was also published in 2005, providing an evidence-based approach to the diagnosis and management of anaphylaxis [3^{••}].

Prevalence of anaphylaxis

Due to lack of consensus on its definition, the exact incidence and prevalence of anaphylaxis has not been well defined. Previously, the incidence of anaphylaxis was estimated to be less than 1% based on medical records in Olmsted County, Minnesota (1983–87) [4]. A recently published study, however, estimated longitudinal healthcare utilization for allergic diseases. Trend analysis performed in the United Kingdom (1990–2004) revealed that rates of hospital admission increased by 700% for anaphylaxis over this time period and by 500% for food allergy, not including emergency department

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Table 1 Diagnostic clinical criteria for anaphylaxis

Anaphylaxis is highly likely when any one of the following three conditions exists:

1. Acute onset of symptoms (minutes to several hours) with mucocutaneous involvement AND one of the following:
 - a. Respiratory compromise
 - b. Reduced blood pressure or associated symptoms of end-organ dysfunction (hypotonia, syncope, incontinence)
2. Two or more of the following that occur after exposure to a *likely* allergen for that patient (minutes to several hours):
 - a. Mucocutaneous involvement
 - b. Respiratory compromise
 - c. Reduced blood pressure or associated symptoms
 - d. Persistent gastrointestinal symptoms
3. Reduced blood pressure after exposure to *known* allergen for that patient (minutes to several hours):
 - a. Infants and children ≤ 10 years: low systolic blood pressure (age-specific) or $>30\%$ decrease in systolic blood pressure*
 - b. Children ≥ 11 years and adults: systolic blood pressure of <90 mmHg or $>30\%$ decrease from that person's baseline

Adapted from [2**] (p. 393).

* Low systolic blood pressure for children is defined as <70 mmHg from 1 month to 1 year, <70 mmHg + $(2 \times \text{age})$ from 1 to 10 years.

visits [5*]. In addition, admission rates for anaphylaxis increased sevenfold from five to 36 per million, which was reflected in all age groups. The number of prescriptions for anaphylaxis also increased 12-fold since 1991.

Physician knowledge

Due to the life-threatening nature of anaphylaxis, rapid recognition and delivery of appropriate therapy by medical personnel are essential to prevent mortality and morbidity. Prior clinical studies [6–8], however, have revealed knowledge deficits among physicians. A retrospective review [9] of 15 North American emergency departments evaluated management of insect sting allergy. Of 617 patients, 31% had multiorgan system involvement or hypotension. Only 12% of systemic reactions were treated with epinephrine and 27% of systemic reaction patients received a prescription for self-injectable epinephrine at discharge.

Gaps have also been identified among primary care physicians. Food allergy is not an uncommon pediatric disease, affecting 6% of young American children [10] and accounting for $\sim 30\,000$ anaphylactic reactions each year in the United States [4]. A survey [11*] of a national random sample of pediatricians in the United States assessed their preparedness to manage food-induced anaphylaxis. Survey questions were based on a clinical scenario involving a child having an anaphylactic reaction after ingesting peanut. About half (56%) agreed with both diagnosis of anaphylaxis and treatment with epinephrine. Most pediatricians (70%) did not recognize that anaphylaxis requires a 4–6-h observation period after resolution of symptoms. This appears to be an international issue. Survey data revealed remarkable undertreatment of children with anaphylaxis by pediatricians in Germany [12]. Of 103 reactions, 76% were classified as grade III ('severe systemic reaction with pulmonary symptoms') or grade IV ('shock including cardiovascular collapse'). Only 21% of these patients, however, received epinephrine: seven intravenously and nine by inhalation. No patient received intramuscular epinephrine. Only 17% of children were prescribed an adrenaline

self-injector. General practitioners in Portugal were surveyed about diagnostic and therapeutic aspects of anaphylaxis using a brief multiple-choice questionnaire [13]. Correct answers for diagnostic aspects ranged from 36 to 46%. While 37% correctly identified injectable epinephrine as the first drug to be administered in acute anaphylaxis, only 18% recognized that the preferred route for administration is intramuscular (36% answered subcutaneous). Clearly, deficits in knowledge of anaphylaxis exist among physicians likely to encounter anaphylaxis.

Education of healthcare professionals is the key to provision of optimal patient care and to maximize patient safety. To assist medical personnel with treatment and long-term management of anaphylaxis, two recent publications are of special note. An examination of 'quandaries' and various clinical scenarios that physicians may encounter in their clinical practice provides thoughtful insight [14**]. Additional perspectives regarding long-term management of anaphylaxis propose a wider range of responsibility for physicians to provide a thorough risk assessment and individualized risk-reduction strategies for affected patients [15*].

Parental knowledge and use of epinephrine

Anaphylaxis frequently occurs outside the hospital setting. Therefore, rapid treatment with epinephrine can be initiated by the patient, caregiver or bystander using auto-injectable devices. Even when auto-injectable epinephrine is prescribed, however, it appears to be underused, as suggested by a recent questionnaire survey [16] of members of a major British patient resource group for people with severe allergic reactions. This prospective evaluation describes 126 reactions in 109 respondents, the majority of whom were children. Foods were implicated in 89% of reactions. Throat–mouth swelling as a symptom was reported in 44% of children and 68% of adults. An adrenaline kit was available at the time of the reaction in more than 75% but was administered only in 11% of children and 32% in adults. Although the data rely on self-report, they suggest that epinephrine is

underused in severe reactions. Another prospective study [17] evaluated parental knowledge and use of epinephrine autoinjectors for children with food allergy. Less than half (48%) of parents were able to cite more than one usual symptom for which epinephrine is indicated. Parental knowledge of how to use epinephrine autoinjectors was not assessed, but proper use was 'demonstrated' to 90% of families by physicians, pharmacists or nurses. Demonstration with a trainer, however, was performed for only 76% of parents.

In an effort to determine factors contributing to underuse of epinephrine autoinjectors [specifically EpiPen (Dey LP, Napa, California)], parents of children with food allergy were surveyed [18[•]]. Of 165 respondents, anaphylaxis was reported in 42% of children. Factors correlating with parental comfort with EpiPen administration included: prior administration of EpiPen by the parent; prior EpiPen training; and parental sense of empowerment as a psychological resource. Parental knowledge of EpiPen use and anaphylaxis did not contribute to increased comfort with EpiPen use.

Demonstration or training appears to be an important factor in encouraging use of epinephrine autoinjectors. Nonetheless, a survey [19] of 1887 members who recently joined the Food Allergy and Anaphylaxis Network found that autoinjectable epinephrine training was incomplete or absent (77%) at the time of the initial prescription. Verbal counseling was lacking in 87% at the time of the initial prescription. Only 13% received training for epinephrine use. The respondents, however, were receptive to the idea of pharmacist-provided education and training.

Delivery/device issues

Previous studies [20] have concluded that intramuscular administration of epinephrine results in earlier and higher peak plasma concentrations than are observed for subcutaneous administration. A recent study [21[•]] investigated whether the needle length of the EpiPen autoinjector is sufficient to penetrate muscle in adults of both sexes. The study population included adults who had height and weight measurements within 6 months of a computed tomography (CT) of the leg. The distance from skin to muscle was digitally measured 50 mm inferior to the ischial tuberosity at the anterolateral thigh. Fifty men and 50 women were included. While only 2% of the men had skin-to-muscle distances greater than the needle length of the EpiPen (1.43 cm), 42% of women's measurements exceeded this value. These findings persisted after the investigators took compression of subcutaneous tissues (by applied pressure with EpiPen use) into account. EpiPen use in many women may result in subcutaneous not intramuscular deposition. These findings, especially in the context of the obesity epidemic, indicate the need to modify the needle length of this device.

As fear/dislike of needles appears to be a common reason for autoinjector underuse, alternative delivery systems are especially desirable for treatment of anaphylaxis. A group has investigated the feasibility and pharmacokinetics of sublingual rapidly disintegrating epinephrine tablets [22^{••}]. Sublingual administration offers the advantages of rapid absorption into the venous circulation while bypassing the gastrointestinal tract and hepatic first-pass metabolism. Using an in-vivo (rabbit) model, the sublingual dose needed to achieve plasma concentrations comparable to those achieved with intramuscular administration was determined. Sublingual absorption followed first-order kinetics and a 40-mg dose was associated with plasma concentrations [peak, time to peak, and area under the curve (AUC)] similar to those obtained with 0.34 mg epinephrine given intramuscularly. They also found that certain expedients [23] can alter bioavailability [23]. Based upon these findings, further development and evaluation of sublingual delivery of epinephrine is certainly warranted.

For years, EpiPen has been the only available autoinjector therapy for treatment of anaphylaxis in the United States. In August 2005, Verus Pharmaceuticals (San Diego, California) launched Twinject. This epinephrine auto-injector is the only available product approved by the FDA that contains two doses of epinephrine in a single, compact device.

School/day-care issues

Little information exists regarding management of anaphylaxis in nonclinical settings such as schools and day-care centers. The Massachusetts Department of Public Health conducted a project [24^{••}] to study anaphylaxis in public school districts in their state. Of 109 school districts, 48 reported epinephrine administration at least once, while 22 school districts reported two or more instances of epinephrine use. Forty-six percent of those receiving epinephrine were elementary school students. The classroom was the most common site in which allergic reactions occurred. In 24% of cases, school personnel were unaware of the child's allergy and had no individualized physician order or care plan in place. Epinephrine was almost always administered by a registered nurse in the health office in which epinephrine was stored. The mean time from symptom onset to epinephrine administration was 10 min with a range of 0–75 min. The average response time was 5 min less for those with a known allergy diagnosis, but there was no difference in response time for reactions that were more severe or for those that occurred outside of the school building, such as in the playground. Of note, 8% of individuals were not transported to an emergency department. These findings highlight the need for a physician-signed health plan available in the school and for trained informed school personnel who can respond appropriately, including

contacting emergency medical personnel for assistance and transport to an emergency department. This study provides valuable data that will be useful for policy development.

Another Massachusetts study [25^{*}] assessed the demographics of schoolchildren who had prescriptions for epinephrine at school. School nurses in three school districts were surveyed. Interestingly, white children were nearly five times more likely to have been prescribed epinephrine than nonwhite children for peanut/tree nut allergy and nearly nine times more likely for stinging insect allergy. Those children from affluent areas were prescribed epinephrine at a rate eight times higher than that for mostly minority children living in economically depressed urban communities. These findings point to possible under-recognition and under-treatment of disadvantaged minority children with allergic disorders for which epinephrine is indicated.

Similarly, investigators in Canada [26] studied the relationship between low socioeconomic status and anaphylaxis management plans in Toronto schools. Principals, rather than nurses, were surveyed. Students in low-income neighborhoods were 2.2 times more likely to have no emergency medications for allergic reactions at school. Staff training was not affected by neighborhood income; 50% of schools reported that their entire staff was trained in EpiPen administration. Taken together, these findings highlight that socioeconomically disadvantaged students are at risk for under-treatment of anaphylaxis and that a significant proportion of school staff lack training in anaphylaxis management. The authors propose that government subsidies for epinephrine autoinjectors be instituted for low-income households.

A national survey of school nurses was conducted to examine school preparedness for various emergencies, including anaphylaxis [27]. Anaphylaxis ranked ninth among reported school emergencies. Seventy-six percent of schools had epinephrine autoinjectors available and this did not differ among inner-city and rural/suburban schools. Eighty-two percent of school nurses reported confidence in managing anaphylaxis, and years of nursing experience did not affect this response. A Scottish study [28] found that schools with students known to be at risk were well prepared, while those without at-risk students often lacked trained staff and typically had no epinephrine on site.

While most studies focused on schools, one novel study [29^{••}] evaluated anaphylaxis practices in child-care centers and also tested an educational intervention. Forty-two centers in Chicago suburbs caring for children aged 1–6 years participated. Nearly all centers reported reliance on parents' providing medications for allergic

reactions and did not otherwise have such medications available. Many centers surveyed had an EpiPen that was kept locked (68%) or in another room (44%). An average of eight providers per center were trained to administer EpiPen. The intervention consisted of an anaphylaxis presentation, EpiPen trainer demonstration and a question-and-answer session. After the intervention, 77% of centers responded that they would administer EpiPen for a severe reaction compared with 24% who would have done so before the seminar. Centers also demonstrated improvement in recognition of anaphylaxis symptoms and proper use of EpiPen. This study demonstrated that an educational intervention may be an effective means to improve anaphylaxis practices at child-care centers.

In Omaha, Nebraska, nurses and select school staff were trained in the recognition of manifestations of anaphylaxis and severe asthma, cardiopulmonary resuscitation and administration of EpiPen and nebulized albuterol [30]. Trainee knowledge was assessed via written examinations and demonstration of medication administration. This study demonstrated the feasibility of implementation of a school-based emergency response protocol.

Access/availability issues

An international survey [31^{*}] of allergist members of the World Allergy Organization (representing 39 countries) was performed to assess epinephrine availability. Availability of dose-appropriate autoinjectors was quite low, ranging from 0% for infant doses to 44% for child doses and 56% for adult doses. Countries in Asia, South America and Africa reported limited availability. Physician prescription was required in 91% of countries in which autoinjectors were available. Twenty-seven percent of countries lacked government or private insurance subsidies for epinephrine autoinjectors. In several countries, the cost of an autoinjector exceeded 1 month's salary. In all, this study highlights the global need for affordable epinephrine autoinjectors, greater availability of such devices and the development of an infant-appropriate product. Such issues of lack of affordability of EpiPen in New Zealand were recently reviewed [32]. The authors urge that epinephrine auto-injectors be subsidized for individuals at risk of anaphylaxis.

Conclusion

Epinephrine is the primary therapy for anaphylaxis, yet studies show that it is underutilized. A variety of contributory factors have been identified, including lack of consensus regarding anaphylaxis diagnosis and management, gaps in knowledge among physicians and patients, limitations in the delivery system for epinephrine administration, and lack of access. Future research should take these issues into account in order to improve the care of individuals with this potentially life-threatening disorder.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 129).

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