The Role of Epinephrine in the Treatment of Anaphylaxis

Anne K. Ellis, MD, and James H. Day, MD, FRCP(C)

Address
Division of Allergy, Kingston General Hospital, 76 Stuart Street, Kingston, ON K7L 2V7, Canada.
E-mail: ellisa@kgh.kari.net

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Epinephrine is the cornerstone of anaphylaxis management. Its administration should be immediate upon evidence of the occurrence of anaphylaxis. Delays in administration may be fatal. The most appropriate administration is 0.3 to 0.5 mL of 1:1000 dilution intramuscularly for adults and 0.01 mg/kg for children, given in the lateral thigh. Patients with known anaphylactic reactivity should be prescribed an epinephrine auto-injector to be carried at all times for treatment of potential recurrences. Education of the patient or parent regarding the proper use of this tool is paramount.

Introduction

Anaphylaxis is the clinical syndrome representing the most severe of systemic allergic reactions. It results from immunologically induced mast cell or basophil mediator release after exposure to a specific antigen in previously sensitized persons, with release of pre-formed mediators stored in granules (especially histamine). The release of these mediators results in smooth-muscle spasm, an increase in vascular permeability, vasodilation, myocardial depression, and reflex activation of vagal effector pathways, leading to the classic features of anaphylaxis, which include some combination of flushing; urticaria and angioedema; wheezing; hypotension; nausea; vomiting; diarrhea; and myocardial ischemia [1].

Epinephrine has a pivotal role as first-line treatment for acute anaphylaxis [1–4]. Although other medications play an auxiliary role in the management (H1 and H2 antagonists, corticosteroids, beta-2 agonists), their use is not discussed here. In this article, the mechanism of action of epinephrine, the appropriate dosing, the route of administration (including discussions concerning the use of intravenous epinephrine), and the use of epinephrine auto-injectors for out-of-hospital anaphylaxis are reviewed.

Beneficial Effects of Epinephrine in Anaphylaxis

Epinephrine is both an alpha (α) and a beta (β) adrenergic receptor agonist. Through α-adrenergic stimulation, epinephrine increases peripheral vascular resistance, improving blood pressure and coronary artery perfusion, reversing peripheral vasodilation, and decreasing angioedema and urticaria [5]. β-1 adrenergic stimulation has positive inotropic and chronotropic effects on the myocardium, and β-2 adrenergic effects include bronchodilation [6]. β-adrenergic receptors also increase intracellular cyclic adenosine monophosphate (cAMP) production in mast cells and basophils, which inhibits further inflammatory mediator release [7,8].

Dosage and Routes of Administration for Epinephrine

Some discrepancy exists in the literature concerning the appropriate dosage of epinephrine for anaphylaxis. Most North American references suggest 0.3 to 0.5 mL of a 1:1000 dilution (0.3 to 0.5mg) [9–14], whereas British and European literature tends to suggest higher doses of 0.5 to 1.0 mg for most adult patients [2–4,15]. Almost all references, however, have concordance with a dosing scheme of 0.01 mg/kg in pediatric patients [2–4,16•,17]. This dose can be repeated, if necessary, until clinical improvement or symptoms of hyperadrenalism (*eg*, palpitations, tremor, uncomfortable apprehension, anxiety) occur.

Until recently, the subcutaneous (SC) route was accepted as equally efficacious as intramuscular (IM) administration, although the British and European literature has always advocated the IM route [18]. Subcutaneous absorption of medication, however, is highly dependent on cutaneous blood flow, which is already compromised in anaphylaxis, and can be aggravated further by epinephrine administration, given its known potent vasoconstrictor activity [19]. Recently, consensus guidelines released by a United Kingdom project team [3] universally recommended IM administration of epinephrine, supported by ensuing letters to the editor [20,21]. Recent studies have demonstrated definitively that the IM route in both children [22•] and adults [23•] yielded a faster onset to peak absorption and

significantly higher plasma epinephrine levels than the SC route. An important finding from the adult study was that IM absorption was superior when administered into the thigh as opposed to the deltoid region. Therefore, the current recommended route of administration of epinephrine is an IM injection into the lateral aspect of the thigh.

Intravenous epinephrine

Perhaps the single remaining controversy in the management of anaphylaxis lies in the appropriate indication for intravenous administration of epinephrine. Many authors caution that intravenous epinephrine is potentially hazardous as it can produce potentially fatal tachyarrhythmias, myocardial infarction, and other complications such as intracerebral hemorrhage [24–26]. In spite of the inherent dangers of this route, there is an acknowledged clinical role for this mode of administration. Increasingly, management articles now endorse the use of intravenous epinephrine for serious cases of anaphylaxis, in which intravascular volume is severely depleted with associated hypotension, or there is significant airway compromise, to achieve the rapid, optimal absorption of epinephrine [18,27]. Ideally, there should be electrocardiographic monitoring available, and the procedure should be undertaken by experienced personnel only.

The most appropriate dosing of intravenous epinephrine is perhaps one of the other reasons for a lack of enthusiasm by certain authors, as no consensus exists in the literature on this issue. Frequently cited [18] is the suggestion by Barach *et al*. [5] of using a 1:100 000 dilution given at 1 to 2 mL (10–20 mg) per minute at an initial dose of 0.75 to 1.5 mg/kg. This may be followed by an infusion if prolonged treatment is required. The additional dilution to 1:100 000 is thought to enhance the safety of the intravenous route. Alternatively, other authors suggest using 1- to 5-mL aliquots of 1:10 000 dilution with or without an ensuing infusion of 1 to 4 mg/min [2,28].

Clearly, the rapid administration of IM epinephrine remains the most important treatment for anaphylaxis. When necessary, careful IV administration of epinephrine for severe anaphylaxis with profound hypotension should be considered.

Unconventional administration routes for epinephrine

Other routes of administration of epinephrine have been tested in an experimental setting, including the inhaled, conjunctival, and sublingual routes. Inhaled epinephrine studies have yielded conflicting results. One report showed that epinephrine was present systemically after an inhaled dose of 3 mg, but not a dose of 1.5 mg, and that the clinical effect was less pronounced and shorter lasting than after SC administration of 0.5 mg epinephrine SC in the upper arm [29]; however, another study demonstrated the converse [30]. The inhaled route consistently produced a more rapid fall in epinephrine levels, and baseline levels were reached within 10 minutes. SC administration, however, was associated with a rise to peak epinephrine concentration by 4 minutes and sustained elevation of arterial epinephrine concentrations over the ensuing 60 minutes of study. Administration of epinephrine via eye drops has been shown to be completely ineffective [29]. A recent pilot animal study [31] evaluated the possibility of sublingual administration of epinephrine, and preliminary results demonstrate epinephrine absorption from a 10-mg sublingual tablet to be comparable with an IM injection of 0.03 mg of epinephrine in rabbits.

In view of these studies, the literature does not support the use of inhaled or conjunctival administration of epinephrine. Sublingual epinephrine is a promising alternative but it is still in early pre-clinical phases of testing.

Epinephrine and concomitant beta-blockade

An anaphylactic state in persons receiving concurrent beta-blocker therapy may not respond to treatment. Anaphylaxis in these patients may be especially severe, protracted, and resistant to conventional treatment. Beta-blockers modify the expected anti-anaphylactic actions of epinephrine, which are mediated through β1 and β2 adrenoceptor stimulation, thereby facilitating unopposed α-adrenergic and reflex vagotonic effects that can lead to augmented mediator release, including bronchoconstriction and bradycardia. Unopposed α-adrenoceptor activation in the presence of excessive adrenaline may also constrict coronary arteries and dangerously exaggerate epinephrine's systemic pressor effects [32].

Epinephrine auto-injectors

All patients who have experienced a documented episode of anaphylactic reactivity should be prescribed, and instructed in the use of, an epinephrine auto-injector. Currently, the EpiPen and the EpiPen Jr. (Dey; Napa, CA) are the only commercially available auto-injectors of epinephrine for patient use, as the preloaded epinephrine syringe (Ana-kit) is no longer manufactured [33]. Both models provide a standardized dose injection IM, and the package insert instructs the patient to inject into the thigh [34], thus providing the established ideal route of administration. The EpiPen provides 0.3 mg of epinephrine and is usually prescribed to adults and children weighing more than 30 kg. The EpiPen Jr. contains 0.15 mg of epinephrine, which is an ideal dose for a child weighing 15 kg, but would overdose a lighter child and underdose a heavier child, given the appropriate dosing of epinephrine in children at 0.01mg/kg. In practice, both the EpiPen and the EpiPen Jr. have been dispensed over almost the entire age range of the pediatric population from birth to adolescence, suggesting that possible overdosing and underdosing occur [35–37]. A study by Simons *et al*. [35] attempted to establish which of the two auto-injectors was preferable in the weight category 15 to 30 kg, for which there is little

information, although some have recommended switching to the adult EpiPen if the child is 20 kg [38] or 25 kg [39]. The EpiPen dose was associated with a better pharmacologic effect but a significantly increased side-effect profile (*eg*, pallor, tremor, anxiety, palpitations) compared with the EpiPen Jr. Therefore, there is no optimal auto-injector for children in this weight category, and the development of additional pre-measured, fixed-dose injectors has been recommended [35,40], but not implemented at this writing. In healthy children, however, the balance of risks and benefits usually falls toward overdosing, because the side effects are usually well tolerated, as opposed to underdosing, which could be fatal.

An alternative to the use of an auto-injector would be the prescription of an ampule of epinephrine with needle and syringe for more accurate dosing of epinephrine for management of anaphylaxis in infants. This method was evaluated prospectively and was shown to result in longer times to draw up the dose and more errors in dose accuracy by parents compared with healthcare professionals [40]. However, given the lack of available user-friendly auto-injectors in doses appropriate for infants, little alternative exists for parents of infants at risk for anaphylaxis.

In addition to the dosing difficulty in the pediatric population, the EpiPen, which is the auto-injector of choice for most adults, may not contain a sufficient dose for adults with anaphylactic reactivity. A retrospective analysis of 105 cases of anaphylactic reactions of varying severity demonstrated that a significant proportion (35%) of patients required more than one injection of epinephrine [41], regardless of the initial dose (median, however, was 0.3 mL of 1:1000 dilution). This problem could be remedied by the development of an auto-injector that contained two doses, but such a product is currently unavailable. Therefore, physicians recommend that patients at risk carry two auto-injectors at all times.

Once prescribed, proper instruction must be imparted to the patient and family regarding the correct indications for and administration of auto-injectors. EpiPens tend to be underutilized or improperly used by those who are prescribed the device. A retrospective analysis by Gold and Sainsbury [42] demonstrated that in children with recurrent anaphylaxis, the prescribed EpiPen was only administered in 29% of cases, and that parental knowledge of the recognition of symptoms of anaphylaxis and proper use of the EpiPen was deficient. In those patients who did receive appropriate administration of their EpiPen, the subsequent need for epinephrine and admission to hospital was reduced, thereby emphasizing the benefits of therapy with auto-injectors.

Of particular concern, however, is that although awareness of the need for patient education is increasing, a recent study reported that of physicians who commonly prescribe auto-injectors (emergency room physicians, pediatricians, and family practitioners), only 25% could correctly demonstrate the proper technique for use [43]. In addition, 76% did not know the two available dose strengths for EpiPens, and 86% did not have a placebo trainer with which to educate their patients. Another study found that only 21% of staff pediatricians could correctly demonstrate the use of an EpiPen [44]. Therefore, more education regarding the correct use of epinephrine auto-injectors is clearly needed at all levels, from medical professionals to parents to patients.

A hazard of epinephrine auto-injectors is accidental digital injection of epinephrine, which can cause significant vasospasm and digital ischemia. Two cases have been reported, and both were successfully treated with either locally applied nitropaste [45] or infiltrated phentolamine (0.5%) [46].

Therefore, although epinephrine auto-injectors can be life-saving for patients with previously documented anaphylaxis, many issues impede their becoming ideal for management of recurrent anaphylaxis. Appropriate dosing in children is problematic given the presence of only two available doses in auto-injector form. Given that a significant proportion of patients experiencing anaphylactic reactivity require more than one dose of epinephrine to manage symptoms, patients should probably be prescribed, and instructed to carry, more than one auto-injector. Finally, patient and, therefore, physician education on the appropriate indications for, and administration of the auto-injector is mandatory, and all physicians who prescribe auto-injectors should have at their disposal a placebo trainer, which is available free of charge from the manufacturer (Dey, Napa CA).

Conclusions

Epinephrine is the cornerstone of management for acute anaphylaxis. The most appropriate administration is 0.3 to 0.5 mL of 1:1000 dilution IM for adults and 0.01mg/kg for children, given in the lateral thigh. This should be given early, and repeatedly if necessary. Severe anaphylaxis with hypotension and other evidence of circulatory collapse should be managed with IV epinephrine, and carefully monitored. Auto-injectors of epinephrine must be prescribed to patients after recovery for possible recurrence of anaphylaxis, and patients or parents should be educated regarding their proper use.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Ellis AK, Day JH: **Anaphylaxis: diagnosis and treatment.** *Allergy Asthma.* 2000, **13:**22–35.
2. Fisher M: **Treatment of acute anaphylaxis.** *BMJ* 1995, **311:**731–733.

3. Project Team of the Resuscitation Council (UK). Consensus Guidelines: **Emergency medical treatment of anaphylactic reactions.** *Resuscitation* 1999, **41:**93–99.
4. Galavas M, Sadana A, Metcalf S: **Guidelines for the management of anaphylaxis in the emergency department.** *J Accid Emerg Med* 1998, **15:**96–98.
5. Barach EM, Nowak RM, Lee TH, Tomlanovich MC: **Epinephrine for the treatment of anaphylactic shock.** *JAMA* 1984, **251:**2118–2122.
6. Brown AT: **Anaphylactic shock: mechanisms and treatment.** *J Accident Emerg Med* 1995, **12:**89–100.
7. Stoloff R, Adams SL, Orfan N, *et al.*: **Emergency medical recognition and management of idiopathic anaphylaxis.** *J Emerg Med* 1991, **10:**693–698.
8. Harvey SC: **Sympathomimetic drugs.** In *Remington's Pharmaceutical Sciences.* Edited by Osol A. Easton: Mack Publishing, 1980:815–824.
9. Bochner BS, Lichtenstein LM: **Anaphylaxis.** *N Engl J Med* 1991, **324:**1785–1790.
10. Wyatt R: **Anaphylaxis: how to recognize, treat, and prevent potentially fatal attacks.** *Postgrad Med* 1996, **100:**87–99.
11. Atkinson TP, Kaliner MA: **Anaphylaxis.** *Med Clin North Am* 1992, **76:**841–855.
12. Friday GA Jr, Fireman P: **Anaphylaxis.** *Ear Nose Throat J* 1996, **75:**21–24.
13. Kagy L, Blaiss MS: **Anaphylaxis in children.** *Pediatr Ann* 1998, **27:**727–734.
14. Freeman TM: **Anaphylaxis: diagnosis and treatment.** *Prim Care* 1998, **25:**809–817.
15. Joint Formulary Committee: **Allergic emergencies.** In *British National Formulary.* London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 1996:130.
16.• Project Team of the Resuscitation Council (UK): **Update on the emergency medical treatment of anaphylaxis for first medical responders and for community nurses.** *Emerg Med J* 2001, **18:**393–395.

Most recent and best published consensus guidelines on the management of anaphylaxis.

17. Anonymous: **Adrenaline for anaphylaxis.** *Drug Ther Bull* 1994, **32:**19–21.
18. Brown AFT: **Therapeutic controversies in the management of acute anaphylaxis.** *J Accid Emerg Med* 1998, **15:**89–95.
19. Hoffman BB, Lefkowitz RJ: **Catecholamines, sympathomimetic drugs and adrenergic receptor antagonists.** In *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* 9th edn. Edited by Hardman JG, Limbird LE, Molinoff PB, et al. New York: McGraw-Hill Companies; 1996:204–209.
20. Sadana A, O'Donnell C, Hunt MT, Gavalas M: **Managing acute anaphylaxis.** *BMJ* 2000, **320:**937.
21. Hughes G, Fitzharris P: **Managing acute anaphylaxis.** *BMJ* 1999, **319:**1–2.
22.• Simons FER, Roberts JR, Gu X, Simons KJ: **Epinephrine absorption in children with a history of anaphylaxis.** *J Allergy Clin Immunol* 1998, **101:**33–37.

Key publication that establishes the superiority of an intramuscular route for the administration of epinephrine.

23.• Simons FER, Gu X, Simons KJ: **Epinephrine absorption in adults: intramuscular versus subcutaneous injection.** *J Allergy Clin Immunol* 2001, **108:**871–873.

Key publication that establishes the superiority of an intramuscular route for the administration of epinephrine.

24. Brueton MJ, Lortan JE, Morgan DJR, Sutters CA: **Management of anaphylaxis.** *Hosp Update* 1991, **17:**386–398.
25. Lip GYH, Metcalfe MJ: **Adrenaline in allergic emergencies.** *BMJ* 1992, **304:**1443.
26. Costa AJ: **Anaphylactic shock.** *Postgrad Med* 1988, **83:**368–373.
27. Fisher MM: **Treating anaphylaxis with sympathomimetic drugs.** *BMJ* 1992, **305:**1107–1108.
28. **Part 8: Advanced challenges in resuscitation section 3: special challenges in ECC 3D: anaphylaxis.** *Resuscitation* 2000, **46:**285–288.
29. Dahlof C, Mellstand T, Svedmyr N: **Systemic absorption of adrenaline after aerosol, eye-drop and subcutaneous administration to healthy volunteers.** *Allergy* 1987, **42:**215–221.
30. Mellem H, Lande K, Kjeldsen SE, *et al.*: **Faster and more reliable absorption of adrenaline by aerosol inhalation than by subcutaneous injection.** *Br J Clin Pharmacol* 1991, **31:**677–681.
31. Gu X, Simons KJ, Simons FER: **Is epinephrine administration from a sublingual tablet feasible for the out-of-hospital first aid treatment of anaphylaxis? Absorption studies in an animal model [abstract].** *J Allergy Clin Immunol* 2002, **109 (1 Part 2):**788.
32. Toogood JH: **Beta-blocker therapy and the risk of anaphylaxis.** *Can Med Assoc J* 1987, **136:**929–933.
33. *Physicians' Desk Reference.* Montvale, NJ: Medical Economics, 2001. http://www.pdr.net/pharm.
34. *EpiPen package insert:* Manufactured by Meridian Medical Technologies Inc., Columbia, MD.
35. Simons FER, Gu X, Silver NA, Simons KJ: **EpiPen Jr versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis.** *J Allergy Clin Immunol* 2002, **109:**171–175.
36. Simons FER, Peterson S, Black CD: **Epinephrine dispensing for the out-of-hospital treatment of anaphylaxis in infants and children: a population-based study.** *Ann Allergy Asthma Immunol* 2001, **86:**622–626.
37. Sicherer SH: **Self-injectable epinephrine: no size fits all!** *Ann Allergy Asthma Immunol* 2001, **86:**597–598.
38. **American Academy of Allergy Asthma and Immunology Board of Directors: Anaphylaxis in schools and other child care settings.** *J Allergy Clin Immunol* 1998, **101(Suppl):**S465–S528.
39. **Canadian Pediatric Society Allergy Section position statement: Fatal anaphylactic reactions to food in children.** *Can Med Assoc J* 1994, **150:**337–339.
40. Simons FER, Chan ES, Gu X, Simons KJ: **Epinephrine for the out-of-hospital (first aid) treatment of anaphylaxis in infants: Is the ampule/syringe/needle method practical?** *J Allergy Clin Immunol* 2001, **108:**1040–1044.
41. Korenblat P, Lundie MJ, Danker RE, Day JH: **A retrospective study of epinephrine administration for anaphylaxis: How many doses are needed?** *Allergy Asthma Proc* 1999, **20:**383–386.
42. Gold MS, Sainsbury R: **First aid anaphylaxis management in children who were prescribed an epinephrine autoinjector device (EpiPen).** *J Allergy Clin Immunol* 2000, **106:**171–176.
43. Grouhi M, Alshehri M, Hummel D, Roifman CM: **Anaphylaxis and epinephrine auto-injector training: Who will teach the teachers?** *J Allergy Clin Immunol* 1999, **103:**190–193.
44. Sicherer SH, Forman JA, Noone SA: **Use assessment of self-administered epinephrine among food-allergic children and pediatricians.** *Pediatrics* 2000, **105:**359–362.
45. Claudy FR: **Pertinent medical intelligence: accidental digital injection of epinephrine.** *Med Mort J* 1995, **44:**292–293.
46. Hinterberger JW, Kintzie HE: **Phentolamine reversal of epinephrine-induced digital vasospasm.** *Arch Fam Med* 1994, **3:**193–195.