

Review Article

Safety of epinephrine for anaphylaxis in the emergency setting

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BACKGROUND: While epinephrine is the recommended first-line therapy for the reversal of anaphylaxis symptoms, inappropriate use persists because of misunderstandings about proper dosing and administration or misconceptions about its safety. The objective of this review was to evaluate the safety of epinephrine for patients with anaphylaxis, including other emergent conditions, treated in emergency care settings.

METHODS: A MEDLINE search using PubMed was conducted to identify articles that discuss the dosing, administration, and safety of epinephrine in the emergency setting for anaphylaxis and other conditions.

RESULTS: Epinephrine is safe for anaphylaxis when given at the correct dose by intramuscular injection. The majority of dosing errors and cardiovascular adverse reactions occur when epinephrine is given intravenously or incorrectly dosed.

CONCLUSION: Epinephrine by intramuscular injection is a safe therapy for anaphylaxis but training may still be necessary in emergency care settings to minimize drug dosing and administration errors and to allay concerns about its safety.

KEY WORDS: Allergy; Anaphylaxis; Epinephrine; Safety; Cardiovascular side effects

World J Emerg Med 2013;4(4):245–251

DOI: 10.5847/wjem.j.issn.1920-8642.2013.04.001

INTRODUCTION

The National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy Research & Education (FARE; formerly the Food Allergy and Anaphylaxis Network [FAAN]) define anaphylaxis as any serious allergic reaction that is rapid in onset and may cause death. While the treatment approach for anaphylaxis is relatively uniform across age, gender, or comorbidities, confusion still exists about the appropriate indications, timing, dose, and route of administration of epinephrine, or of its safety.^[1-7] Epinephrine by the intramuscular (IM) route is the recommended therapy of choice in current guidelines or consensus statements from the American Academy of Allergy, Asthma & Immunology (AAAAI) anaphylaxis guidelines, the World Allergy Organization (WAO) anaphylaxis guidelines, the NIAID/FARE food allergy

guidelines, and a newer consensus recommendation (the International Consensus ON [ICON] food allergy) from the International Collaboration in Asthma, Allergy and Immunology (iCAALL) group.^[8-11] In a recent study of 1 114 pediatric emergency medicine physicians, 94% correctly identified epinephrine as the treatment of choice for anaphylaxis but only 67% used IM administration, despite the fact that IM administration is the preferred route of administration.^[12] Factors associated with proper IM administration were the presence of a residency training program at the institution and a higher volume of anaphylaxis patient cases. It may also be that some healthcare providers in emergency settings are uncomfortable with using epinephrine first, and are concerned with its safety, and additional training may be necessary on proper dosing and administration to ensure that it is given safely.

Why epinephrine first?

An anaphylactic reaction is resulted when mast cells and basophils systemically and abruptly release mediators of inflammation. Epinephrine, a mixed alpha- and beta-adrenergic receptor agonist, treats anaphylaxis symptoms by alleviating allergen-induced inflammatory and physiologic effects.^[13] The alpha-adrenergic vasoconstricting effect reverses vasodilation, thus alleviating hypotension and reducing erythema, urticaria and angioedema.^[14] Beta-adrenergic receptor agonist activity acts to dilate bronchial airways, increase the force of myocardial muscle contraction (inotropy) and heart rate (chronotropy), which increases cardiac output, and attenuates the severity of IgE-mediated reactions via receptors on mast cells.^[13,15,16] Intramuscular administration allows more rapid peak plasma levels compared with subcutaneous (SC) administration in children or adults.^[17,18]

Why not antihistamines or corticosteroids first?

Antihistamines, such as diphenhydramine, have a longer onset of action and longer time to peak activity compared with epinephrine.^[19,20] The most compelling evidence against the use of H1 blockers as an initial therapy comes from studies looking at the onset of suppression of histamine-induced cutaneous flares. Time to 50% reduction in histamine-induced flare was 52 minutes for IM diphenhydramine, 80 minutes for oral diphenhydramine, and 101 minutes for oral fexofenadine.^[19] We have learned from fatal cases of anaphylaxis that patients are at risk for death in as little as 5 minutes following allergen exposure.^[21-23] Since anaphylaxis can involve multiple organ systems and occur in less time than the onset of action of antihistamines, they should not be used as first-line therapy. This is consistent with current recommendations on antihistamines (and corticosteroids for that matter) positioning them as adjunctive therapies.^[8-11] There is no evidence that they provide life-saving treatment (i.e. they do not prevent or relieve upper airway obstruction, hypotension, or shock).^[24] Antihistamines [IM or intravenous (IV)] are adjunctive therapies and may be tried after epinephrine is administered to help control cutaneous and cardiovascular manifestations, such as itching, flushing, urticaria, angioedema, and nasal and eye symptoms, as well as prevent secondary reactions.^[8-11] Similarly, corticosteroids have the potential to prevent recurrent or protracted episodes, but should not be used in place of, or prior to, epinephrine, as they are not helpful for

acute symptoms.^[8]

It is for these reasons that IM epinephrine is recommended as the treatment of choice for anaphylaxis. Epinephrine may be reserved for patients in shock only or because a clinician is concerned about its safety, when in fact it is indicated and needed to save a patient's life. The objective of this review was to evaluate the safety of epinephrine for patients with anaphylaxis, including other emergent conditions, treated in emergency care settings.

METHODS

A MEDLINE search using PubMed was conducted without limits to identify articles that discuss the dosing, administration, and safety of epinephrine for anaphylaxis in the emergency setting. The authors prospectively decided that studies discussing the use of epinephrine in the emergency medicine setting for anaphylaxis, or other acute respiratory conditions (e.g., acute asthma, bronchiolitis, croup), with positive or negative results, would be considered for inclusion. Articles that explicitly discussed the use of epinephrine for anesthetic applications or for cardiac arrest from trauma or other non-allergic, non-respiratory causes were excluded. The following terms and their combination were used for the search: "food allergy", "latex allergy", "drug allergy", "seafood allergy", "anaphylaxis", "asthma", "respiratory", "epinephrine", "dosing", "inhaled", "nebulized", "emergency department", "safety", "cardiovascular", "side effect", "intramuscular", "intravenous", and "route of administration". Literature describing studies in both the pediatric and adult populations was reviewed. Descriptive statistics were used to summarize the results of each study.

RESULTS

Search results

To ensure that any report on the use of epinephrine in the emergency setting for anaphylaxis or other acute respiratory condition indexed in MEDLINE was captured, we used the key-terms listed above and the combination of these key terms. Redundancies in the searches were purged until we were confident that all results were unique. All results were used for the systematic summary of epinephrine safety here. Our searches yielded both individual and retrospective case reviews in which epinephrine was used in the emergency setting for anaphylaxis ($n=10$) and controlled studies in

the emergency setting where epinephrine was used for other acute respiratory conditions ($n=10$).

Epinephrine dosing and administration for anaphylaxis

Once an initial assessment is made and clinicians are confident in their diagnosis of anaphylaxis, appropriate treatment should be initiated with an IM injection of epinephrine [into the anterolateral aspect of the thigh (vastus lateralis)], quickly followed by placement of the patient in a recumbent position, and the provision of supplemental oxygen and/or the administration of IV fluids, if needed based on the severity of symptoms.^[8] Please refer to available guidelines cited here for a complete overview of management in the acute and long-term settings, and in patients with comorbid conditions including cardiovascular disease.

Epinephrine is available in different doses and concentrations for delivery by different routes, and for different indications, including anaphylaxis and cardiac arrest. The differences, as well as inconsistent labeling of epinephrine vials, can lead to life-threatening medication errors (Table 1). Labeling of epinephrine concentration is sometimes provided in ratios rather than uniformly as a mass of concentrations or percentages. The availability of epinephrine in both 1:1 000 and 1:10 000 concentrations can lead to incorrect dosing in an acute setting.^[5,7] Epinephrine for anaphylaxis is given at doses that are substantially lower than those needed for cardiac arrest (Table 2). If emergency room "crash carts" are stocked only with pre-filled, higher concentration syringes used

Table 1. Factors contributing to dosing errors of epinephrine

Inadequate physician knowledge about the appropriate dose and route of epinephrine administration for anaphylaxis
Lack of IM doses for anaphylaxis on emergency crash carts
Complicated dose calculations involving decimals and ratios
Epinephrine labeled with ratios (1:1 000 and 1:10 000) associated with excessive epinephrine doses and longer delay in dosing vs gram weight/volume concentration labels
Lack of adequate communication between physicians and nurses

Table 2. Dosing of epinephrine in anaphylaxis compared with cardiac resuscitation

Anaphylaxis	Adults: Epinephrine 1:1 000 dilution (1 mg/mL), 0.2–0.5 mL ^[8] Pediatrics: Epinephrine 1:1 000 dilution (1 mg/mL), 0.01 mg/kg, maximum 0.3 mg dosage IM or SC every 5 minutes, as necessary ^[8]
Cardiac arrest	Adults: 1 mg of 1:10 000 dilution IV push ^[6,47]

IM: intramuscular; SC: subcutaneous; IV: intravenous.

for IV push during cardiac arrest, there is a potential for inadvertent excessive dosing in an urgent situation.^[6]

Epinephrine safety in anaphylaxis and other conditions

A literature search in which the safety and cardiovascular effects of epinephrine were discussed in the context of anaphylaxis produces ten case-based reports, which are summarized in Table 3.^[6,25–33] Although the vast majority of reported cardiovascular adverse events with epinephrine occurred with IV dosing, highlighting the need to proceed with caution if considering epinephrine by this route for anaphylaxis, events have been reported with appropriate IM administration. However, the most serious adverse effects with epinephrine occur with IV administration.^[25,31,34] Therefore, the IV route should only be considered in the specific instances discussed below. In some cases, healthcare providers may inappropriately associate epinephrine with a risk for cardiovascular events,^[35] which may delay the use of epinephrine in cases where it is clearly indicated.

A literature search to identify studies in which the safety of epinephrine was discussed in the context of conditions other than anaphylaxis yielded ten studies which are summarized in Table 4.^[36–45] Conditions in which epinephrine was used were described as acute asthma, life-threatening asthma, croup, acute bronchiolitis, and hospitalized bronchiolitis. Administration routes for epinephrine included SC, nebulized aerosol, and IV infusion. Epinephrine dosing was variable and, overall, no serious adverse events were reported. Sinus tachycardia was noted in the study by Smith et al and patients in this study patients received IV epinephrine (3 different dosing strategies). In these 10 studies, epinephrine induced expected side-effects including nausea, dizziness, vomiting, tremor, headache, palpitations, excitement, and pallor, but no life-threatening cardiovascular adverse events were observed. In general, these studies show that epinephrine is safe for patients with urgent medical needs for conditions other than anaphylaxis.

When is IV dosing of epinephrine in anaphylaxis appropriate?

While guidelines recommend that epinephrine be given via IM injection for the initial treatment of anaphylaxis,^[8] IV delivery should be considered in special circumstances such as severely hypotensive patients, patients in cardiac or respiratory arrest, or those

Table 3. Cardiovascular events reported with epinephrine given for anaphylaxis and other conditions

Reports	Patient (s)	IV epinephrine dosing (dilution)	Cardiovascular event (s)
Horak et al, 1983 ^[25]	23 year-old female, penicillin-induced anaphylaxis	0.3 mg	Severe myocardial ischemia
Butte et al, 1999 ^[26]	11 year-old male, croup with severe respiratory distress	0.5 mL (by nebulizer diluted in 3 mL 0.9% saline)	Increased heart rate, ventricular tachycardia, myocardial infarction
Johnston et al, 2003 ^[27]	40 year-old female with reaction to pseudoephedrine and diphenhydramine taken for acute sinusitis (no hypotension or respiratory compromise)	1 mL (1:1 000)	Pulseless ventricular tachycardia
Anchor et al, 2004 ^[28]	1. 60 year-old female, NSAID-induced angioedema 2. 76 year-old male, idiopathic anaphylaxis	1. 0.3 mL (1:1 000) 2. 0.2 mL (1:1 000)	1. Intermittent ventricular tachycardia 2. Immediate blood pressure spike, tachycardia, and nonspecific ST changes by ECG
Arfi et al, 2005 ^[29]	14 year-old male, IVIg-induced anaphylaxis	0.01 mL/kg (1:1 000)	Acute myocardial ischemia
Putland et al, 2006 ^[30]	220 cases with severe asthma (retrospective)	Average epinephrine infusion rate was 1.5 µg/min (range=0.5 to 13.3 µg/min) Total dose range=15 to 99 551 µg Duration of infusion, 10 min to 11.4 days (median 19.5 h)	1. Supraventricular tachycardia (n=2; both SVT) 2. Hypotension requiring treatment (n=4) 3. Objective evidence of myocardial ischemia, elevated troponin (n=2) 4. Sinus tachycardia (n=23) 5. Chest pain without ECG or marker changes (n=2)
Shaver et al, 2006 ^[31]	29 year-old female, penicillin-induced anaphylaxis	0.1 mg (1:10 000)	Acute myocardial infarction
Izgi et al, 2010 ^[32]	37 year-old female, amoxicillin-induced anaphylaxis	1 st dose: 0.5 mg (1:10 000) 2 nd dose: 0.5 mg (1:10 000) 3 rd dose (undiluted): 1 mg (1:1 000)	Severe myocardial ischemia
Kanwar et al, 2010 ^[6]	1. 23 year-old female, seafood anaphylaxis 2. 52 year-old female, seafood anaphylaxis 3. 33 year-old female, IV iron sulfate anaphylaxis 4. 34 year-old male, seafood anaphylaxis	1. 2 doses of 1 mg (1:10 000) 2. 0.3 mg (1:1 000) 3. 0.3 mg (1:1 000) 4. 1 mg (1:10 000)	1. Cardiogenic shock / severe left ventricular dysfunction 2. Severe left-sided chest pain, new-onset ST elevations 3. Right-sided coronary artery dissection 4. Sustained ventricular tachycardia that resolved spontaneously
Cunnington et al, 2013	43 year-old female, flucloxacillin anaphylaxis	2 doses of 0.5 mg (0.5-mL 1:1 000 solution) given intramuscularly	5 minutes following a second dose, the patient complained of typical ischemic chest discomfort. ECG demonstrated 1-mm ST-segment depression in the anteroseptal chest leads. Pain and ECG changes resolved spontaneously after 30 minutes. Labs (6 hours later) showed elevated high-sensitivity troponin I level of 530 ng/L (upper limit of normal 30 ng/L).

ECG: electrocardiogram; IV: intravenous; IVIg: intravenous immunoglobulin; NSAID: non-steroidal antiinflammatory drug; SVT: supraventricular tachycardia.

who have failed to respond to multiple IM injections of epinephrine. In the event that multiple IM injections of epinephrine and aggressive volume replacement do not alleviate hypotension, IV epinephrine and vasopressors may be used. In such cases, continuous hemodynamic monitoring is recommended.^[8]

If IV administration is deemed necessary, the use of a highly diluted solution will best balance efficacy and patient safety.^[8] An epinephrine infusion may be prepared by adding 1 mg (1 mL) of 1:1000 dilution of epinephrine to 250 mL of D5W to yield a concentration of 4 µg/mL. This 1:250 000 solution is infused at a rate of 1 µg/min (15 drops/minute using a micro-drop apparatus [60 drops/min = 1 mL = 60 mL/h]), titrated to desired hemodynamic response, increasing to a maximum of 10 µg/min for adults and adolescents.^[8]

CONCLUSION

It is critically important that any misconceptions regarding the safety and use of epinephrine should be resolved. In this review, we attempt to address two real-world concerns regarding the use of epinephrine in emergency care settings for anaphylaxis: 1) appropriate dosing and administration of epinephrine and 2) epinephrine safety. Consensus recommendations on the use of epinephrine as initial therapy for anaphylaxis are shown in Table 5.^[11] Limitations of this evaluation include the inability to account for the level of expertise a particular clinician has with anaphylaxis or other acute respiratory conditions, or the uniqueness of each emergent situation. Furthermore, the literature, in general, on this subject is relatively limited.

Epinephrine is the therapy of choice for an

Table 4. Safety of epinephrine given for conditions other than anaphylaxis

Reports	Patients	Epinephrine dosing & administration	Efficacy	Adverse effects
Pliss et al. 1981 ^[36]	n=25 Acute asthma Age 17–47 years	0.3 mL 1:1 000 [SC] 0, 20, & 40 minutes (0.9 mg total dose) 0.16 mg epinephrine aerosol 0, 10, 20, 30, 40, & 50 minutes (0.96 total dose)	Parenteral epinephrine superior to inhaled epinephrine for severe asthma (patients with greater degree of obstruction)	No significant differences between groups for change in BP, PR, or RR. 70% [SC group] vs. 17% [inhaled] complained of palpitations or tremor. Parameters approached normal in both groups as treatment progressed
Becker et al. 1983 ^[37]	n=40 Acute asthma Age 6–17 years	0.4 mL 1:1 000 [SC] (0.1 mL/kg, 0.4 mg total dose) 0.5% salbutamol by mask and nebulizer using 100% oxygen (6–10 L/min flow) for 5–10 minutes	No significant difference between groups for pulmonary index, HR, RR, SBP, DBP, FEV1, FVC, percent FEV1/FVC, and FEF 25%–75% (absolute or normalized) Increased HR with salbutamol at 15 and 30 minutes (no change for epinephrine) Decrease in RR with salbutamol (no change for epinephrine) Decrease in DBP with epinephrine	Increased HR with salbutamol at 15 and 30 minutes (no change for epinephrine) Decrease in RR with salbutamol (no change for epinephrine) Decrease in DBP with epinephrine Nausea, vomiting, tremor, headache, palpitations, excitement, and pallor were noted in 50% of patients given epinephrine
Cydulka et al. 1988 ^[38]	n=95 Acute asthma Age 15–96 years (patients with history of recent MI or angina excluded)	0.3 mL 1:1 000 [SC] 0, 20, 40 minutes (0.9 mg total dose)	Regardless of age, SC epinephrine rapidly and effectively reversed hypoxemia and improved pulmonary function	No significant change in HR No increase in ventricular arrhythmias across ages
Ledwith et al. 1995 ^[39]	n=56 Croup with stridor and barking cough Age 0–>60 months	0.5 mL 2.25% racemic epinephrine in 2.0 mL normal saline by nebulizer	Effective with patients having a sustained response to a single dose of racemic epinephrine, but success depended on observation period to manage potential relapse	No adverse events reported and investigators' conclusion was that racemic epinephrine was safe
Lin et al. 1996 ^[40]	n=90 Acute asthma Children	2 mL (5.0 mg) terbutaline in 2 mL 0.9% saline for inhalation over 10 minutes 0.01 mL/kg 1:1 000 epinephrine [SC to deltoid] (maximum 0.3 mL)	The clinical severity score and spirometry of both groups were significantly improved after treatment Epinephrine had better mean oxygen saturation, frequency of oxygen desaturation, and FEF 25%–75% For patients with initial FEV1 <60% of predicted, epinephrine treatment was more effective in the improvement of FEV1, FEF 25%–75%, and oxygen saturation	Significantly more adverse effects occurred epinephrine (47% vs. 11%, $P=0.0002$) which included pallor, tremor, dizziness, headache, palpitation, soreness of legs, numbness of extremities, cold sweating, general weakness and nausea
Plint et al. 2000 ^[41]	n=121 Acute asthma Age 1–17 years	0.03 mL/kg salbutamol (5 mg/mL) made up in 3 mL normal saline given by mask and nebulizer with oxygen at 5 L/min 0, 20, 40 minutes (maximum 1 mL) 0.03 mL/kg racemic epinephrine (20 mg/mL) made up in 3 mL normal saline given by mask and nebulizer with oxygen at 5 L/min 0, 20, 40 minutes (maximum 1 mL)	No significant difference in change in pulmonary index score or oxygen saturation between groups Significantly greater decrease in HR and increase in RR with salbutamol No difference in requirement for supplemental oxygen, length of emergency department stay, admissions, or length of hospital stay	No significant difference in rate of pallor, nausea, increased heart rate, or tremor Patients treated with epinephrine had significantly higher rate of minor adverse effects including excess nasal discharge, cough, sneezing, stinging nostrils, sore throat, and agitation
Smith et al. 2003 ^[42]	n=27 Life-threatening asthma Age 19–58 years	In 24/27 pts. 50 µg loading dose and 1 mg of a 1:10 000 solution (200 µg total dose) 14/24 pts also received continuous IV epinephrine between 3 and 20 µg/min (80% of pts received 1 mg over 1 hour) 3/24 pts received IV epinephrine infusion only, either 1 mg over one hour or 1–2 µg/min for 2 hours (300 µg total dose)	Retrospective chart review of safety only. Efficacy not reported	No patient had an arrhythmia other than sinus tachycardia No major adverse effects No incidences of cardiac ischemia, hypotension, neurologic defect or death Only transient hypertension at intubation that resolved with sedation IV epinephrine safe in young adults with life-threatening asthma
Mull et al. 2004 ^[43]	n=66 Acute bronchiolitis Age 0–10 months	0.9 mg/kg of 2.25% nebulized racemic epinephrine in 2 mL of 0.9% isotonic sodium chloride given by mask with 100% oxygen at 6 L/min 0, 30, 60 minutes 0.15 mg/kg of 0.5% nebulized albuterol sulfate in 2 mL of 0.9% isotonic sodium chloride given by mask with 100% oxygen at 6 L/min 0, 30, 60 minutes	Successfully relieves respiratory distress No significant difference in clinical score, respiratory rate, or room air saturation over time between the groups No significant difference in relapse rate between the groups	Adverse effects occurred infrequently 1 infant vomited from the epinephrine group vs. 5 from the albuterol group 1 infant exhibited pallor in the epinephrine group
Adoun et al. 2004 ^[44]	n=38 Acute severe asthma	3 mg nebulized epinephrine given over 20 minutes 5 mg nebulized terbutaline given over 20 minutes	Equal increase in PEF and decrease in RR between groups No synergism with both agents	No adverse events observed
Langley et al. 2005 ^[45]	n=62 Hospitalized bronchiolitis Age 6 weeks to 24 months	0.5 mL of 2.25% nebulized racemic epinephrine by mask with oxygen at 5–7 L/min q 1–4 h 1.5 mg (>10 kg), 1.25 mg (>6 kg–<10 kg), or 0.75 mg (<6 kg) nebulized albuterol sulfate by mask with oxygen at 5–7 L/min given in 3 mL normal saline q 1–4 h	Successfully relieves respiratory distress without overall significant difference in efficacy between groups Racemic epinephrine significantly better for wheezing on day 2 and entire hospital stay	Adverse events including tremor, vomiting, or pallor were not significantly difference between the groups

BP: blood pressure; DBP: diastolic blood pressure; FEF 25%–75%: Forced expiratory flow between 25% and 75%; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; HR: heart rate; IV: intravenous; PEF: peak expiratory flow; PR: pulse rate; Pts: patients; RR: respiratory rate; SBP: systolic blood pressure; SC: subcutaneous.

Table 5. Consensus recommendations for the treatment of anaphylaxis in the emergency setting^[11]

Epinephrine	Epinephrine, IM; autoinjector or 1:1 000 solution
	Weight, 10–25 kg: 0.15 mg epinephrine autoinjector (IM to anterolateral thigh)
	Weight, >25 kg: 0.3 mg epinephrine autoinjector (IM to anterolateral thigh)
	Epinephrine (1:1 000 solution, 0.01 mg/kg per dose; maximum dose=0.5 mg per dose (IM, anterolateral thigh)
	Epinephrine doses might need to be repeated every 5–15 minutes
	Consider continuous epinephrine infusion for persistent hypotension (ideally with continuous noninvasive monitoring of blood pressure and heart rate); alternatives are endotracheal or intraosseous epinephrine
Others	Place patient in Trendelenburg position
	Bronchodilator (β_2 -agonist; albuterol)
	Metered-dose inhaler (child: 4–8 puffs; adults: 8 puffs) or Nebulized solution (child: 1.5 mL; adult: 3 mL) q 20 minutes or continuously as needed
	H ₁ blocker: less-sedating second-generation antihistamines recommended
	Corticosteroids
	Prednisone at 1 mg/kg with a maximum dose of 60–80 mg orally or
	Methylprednisolone at 1 mg/kg with a maximum dose of 60 to 80 mg IV
	Supplemental oxygen therapy
	IV fluids in large volumes if patients present with orthostasis, hypotension, or incomplete response to IM epinephrine
	Vasopressors (other than epinephrine) for refractory hypotension, titrate to effect
	Glucagon for refractory hypotension, titrate to effect
	Child: 20–30 μ g/kg Adult: 1–5 mg Dose can be repeated or followed by infusion of 5–15 μ g/min
	Atropine for bradycardia, titrate to effect

anaphylactic reaction and, when administered correctly, is safe and effective. Because of the potential for cardiovascular adverse events, IV epinephrine should only be administered for anaphylaxis in profoundly hypotensive patients or patients in cardiac or respiratory arrest who have failed to respond to IV volume replacement and multiple IM doses of epinephrine.

Important points related to treatment of the patient with anaphylaxis include:^[46] 1) epinephrine is first, antihistamines and corticosteroids are adjunctive therapies, and 2) epinephrine should be administered intramuscularly, and not intravenously in concentrations of greater than 1:10 000, and then only as a last resort.

Funding: We received no independent support for this research study.

Ethical approval: Not needed.

Conflicts of interest: We have no conflicts of interest to report.

Contributors: Wood JP proposed the study and wrote the paper.

All authors contributed to the design and interpretation of the study and to further drafts.

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Received April 20, 2013

Accepted after revision October 2, 2013