

Letter to the Editor

Effectiveness of delayed epinephrine in anaphylaxis

To the Editor:

Epinephrine is the treatment of choice for anaphylaxis.¹ Although its role in acute anaphylaxis has been emphasized, the importance of epinephrine in the treatment of protracted anaphylaxis is underappreciated. We report 2 patients with protracted anaphylaxis who benefited from treatment with intramuscular (IM) epinephrine. The first patient had 2 episodes. During the first episode, epinephrine was withheld initially due to concern over significant cardiac risk factors; during the second episode, repeat epinephrine dosing was delayed for the same reason. The second patient had no initial response to a single dose of IM epinephrine or to nebulized epinephrine, but responded to IM epinephrine when treated 48 hours later.

Patient 1 was a 54-year-old white male with significant cardiac risk factors (status post cardiac transplant, coronary artery disease in the transplant with left ventricular dysfunction, history of nonsustained ventricular tachycardia with placement of an automated internal cardioverter-defibrillator, and hypercoagulable state with multiple embolic and thrombotic events). He was chronically anticoagulated with warfarin and was admitted to the hospital for banding of recurrent hemorrhoidal bleeding. The warfarin was held, and he was started on an intravenous (IV) heparin drip (he had tolerated IV heparin 7 months previously). Within 30 minutes, he developed dysphagia with oral, facial, and laryngeal edema. He did not have any dyspnea, nausea, vomiting, diarrhea, abdominal pain, urticaria, pruritus, or hypotension. He was treated acutely with 50 mg IV diphenhydramine and 100 mg IV hydrocortisone. Epinephrine was held because of his significant cardiac risk factors. He was intubated because of laryngeal edema.

The following laboratory results were normal: C3, C4, C1 esterase inhibitor functional assay, white blood cell count, liver and kidney function tests, electrolytes, and cyclosporine level. A latex IgE titer was negative. A chest computed tomography scan was unremarkable except for expected postoperative changes. While in the intensive care unit (ICU), he was treated with scheduled antihistamines (H1- and H2-blockers) and IV methylprednisolone. The heparin was discontinued on ICU day 2. Epinephrine was still held because of his cardiac risk factors. On ICU day 9, he failed an extubation attempt because of persistent significant laryngeal edema and underwent a tracheostomy. The laryngeal edema persisted for over 2 weeks and necessitated continued mechanical ventilation. He did not have any other symptoms. On ICU day 17, the patient was given a single dose of IM epinephrine (1:1000, 0.3 cc). The decision to proceed with epinephrine therapy (for persistent laryngeal edema) despite significant cardiac risk factors was made at that time because potential cardiac side effects had been addressed; he was monitored closely in the ICU, was mechanically ventilated with a secure

airway, and had an implantable cardioverter-defibrillator in place. After epinephrine administration, he had a short run of ventricular tachycardia that lasted several seconds. Within 15 minutes, laryngoscopy showed a dramatic decrease in airway edema and inflammation. He was weaned off the ventilator the same day and had no recurrence of symptoms. His tracheostomy was allowed to heal. He did well until 3 years later, when he developed facial pain, dysphagia, oral swelling, dyspnea, wheezing, nausea, and abdominal pain. He went to his local emergency department and was found to have uvular and oropharyngeal edema. Due to significant worsening during the exam, he was intubated nasally for airway protection and transferred to our hospital's ICU. Recent new medications included gabapentin (started 2 months prior) and prednisolone eye drops (started 10 days prior for an eye infection); he had not received heparin. Repeat complement studies were again normal. On ICU day 1, he was given 1 dose of IM epinephrine (1:1000, 0.3 cc) without any improvement of oropharyngeal edema. The edema persisted, necessitating continued intubation and mechanical ventilation. Further treatment with epinephrine was withheld due to concern over his significant cardiac risk factors until ICU day 6, when he was given IM epinephrine (1:1000, 0.3 cc) every 30 minutes for a total of 3 doses and had a dramatic decrease in his oropharyngeal edema. He had no arrhythmia, and was successfully extubated.

Patient 2 was an 82-year-old white male with known coronary artery disease and diabetes mellitus type II who developed left ocular neovascularization. (This patient was previously reported as 1 of 2 patients with allergic reactions to pegaptanib, a pegylated oligonucleotide and vascular endothelial growth factor antagonist.²) He was treated with topical ocular lidocaine and levofloxacin, which he had previously tolerated. Within 30 minutes of his first dose of intraocular pegaptanib, he developed diffuse urticaria with eye, lip, and tongue edema. He had no dyspnea, nausea, vomiting, diarrhea, abdominal pain, or hypotension. He was treated with a single dose of IM epinephrine (1:1000, 0.3 cc), 50 mg oral diphenhydramine, and 125 mg IV methylprednisolone in the ophthalmology clinic. His symptoms did not improve. After transfer to the emergency department, he was noted to have stridor, wheezing, and hypertension. He received nebulized epinephrine with no response. He was intubated nasally for airway protection and transferred to the ICU. Antihistamines (H1- and H2-blockers) and IV methylprednisolone were given initially and continued regularly in the ICU. He was taking an angiotensin converting enzyme inhibitor as an outpatient; this was discontinued after admission. There was no improvement in his oropharyngeal edema over 48 hours, though the urticaria gradually resolved. On ICU day 2, more than 48 hours after onset of symptoms, he was given a single dose of IM epinephrine (1:1000, 0.3 cc). He had a 50% improvement in

angioedema within 15 minutes. He received a second dose of IM epinephrine (1:1000, 0.3 cc) 4 hours later with complete resolution of oropharyngeal angioedema and successful extubation by the following morning.

Anaphylaxis may be uniphasic, biphasic (an acute episode that resolves with symptoms recurring 4-8 hours later), or protracted in nature.³ Protracted anaphylaxis despite treatment has been reported to last up to 3 weeks.⁴ In 2 series of patients with anaphylaxis, protracted anaphylaxis was seen in 23% (3 of 13) of children with food allergy⁴ and 28% (5 of 25) of adults with food or drug allergy.³

The recommended dosing of aqueous epinephrine for the treatment of anaphylaxis is 0.01 mg/kg up to 0.5 mg IM every 5-15 minutes as necessary.¹ In the case of patient 1, epinephrine was withheld during his first episode of anaphylaxis for over 2 weeks due to concern over his substantial cardiac risk factors. It is possible that the delay in administration of epinephrine contributed to his protracted laryngeal edema. Sampson et al⁴ showed that food-related anaphylaxis not treated with epinephrine before onset of severe symptoms was associated with increased mortality. In addition, a retrospective study in children showed that the median time to initial dose of subcutaneous epinephrine was higher in patients who developed biphasic anaphylaxis compared with those who developed uniphasic anaphylaxis (190 minutes vs 48 minutes).⁵ The possibility of the delay in epinephrine administration to patient 1 contributing to his first episode of protracted anaphylaxis is made less likely by his second episode, in which he developed protracted anaphylaxis despite receiving epinephrine acutely. Similarly, patient 2 had a protracted course despite an initial dose of IM epinephrine and a single dose of nebulized epinephrine.

Physician reluctance to use epinephrine in patients with significant cardiac risk factors is perhaps reinforced by a recent case report that details a patient without prior cardiac disease who developed arrhythmia and probable coronary artery vasospasm after treatment with IV epinephrine for postoperative anaphylaxis.⁶ If significant cardiac risk factors exist (as in both our patients), proper precautions should be taken and careful thought given

prior to administration of epinephrine for the treatment of anaphylaxis. One could consider a lower than maximum dose of epinephrine initially to observe for arrhythmia and response, followed by repeated dosing as clinically indicated. We believe that the existence of significant cardiac risk factors should not preclude the appropriate treatment of anaphylaxis. In other words, cardiac disease should not be considered as an absolute contraindication for the use of epinephrine in treatment of anaphylaxis. Moreover, these 2 patients demonstrate that epinephrine remains the treatment of choice for anaphylaxis, be it in the acute or protracted phase.

Nathaniel D. Hare, MD^{a,b}

Zuhair K. Ballas, MD^{a,b}

From ^athe Department of Internal Medicine, Division of Allergy-Immunology, Department of Internal Medicine, University of Iowa, Iowa City, Iowa; and ^bIowa City VA Medical Center, Iowa City, Iowa. E-mail: Nathaniel-hare@uiowa.edu.

Disclosure of potential conflict of interest: N. D. Hare has consultant arrangements with ZLB Behring, Greer Laboratories, Bio Products, and Lev Pharmaceuticals. Z. K. Ballas has consultant arrangements with Talecris Biotherapeutics, Greer Laboratories, Coley Pharmaceuticals, and Novartis Pharmaceuticals.

REFERENCES

1. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.
2. Steffensmeier AC, Azar AE, Fuller JJ, Muller BA, Russell SR. Vitreous injections of pegaptinib sodium triggering allergic reactions. *Am J Ophthalmol* 2007;143:512-3.
3. Stark BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. *J Allergy Clin Immunol* 1986;78:76-83.
4. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-4.
5. Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. *Pediatrics* 2000;106:762-6.
6. Goldhaber-Fiebert S, Grecu L. Postoperative ST-segment elevation: was vasospasm caused by anaphylaxis or by its treatment with epinephrine? *Ann Allergy Asthma Immunol* 2006;97:449-53.

doi:10.1016/j.jaci.2007.06.008