

Confusion About Epinephrine Dosing Leading to Iatrogenic Overdose: A Life-Threatening Problem With a Potential Solution

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Epinephrine is indicated for various medical emergencies, including cardiac arrest and anaphylaxis, but the dose and route of administration are different for each indication. For anaphylaxis, it is given intramuscularly at a low dose, whereas for cardiac arrest a higher dose is required intravenously. We encountered a patient with suspected anaphylaxis who developed transient severe systolic dysfunction because of inappropriately received cardiac arrest dose, ie, larger dose given as an intravenous push. Three additional patients who experienced potentially lethal cardiac complications after receiving inappropriately higher doses intravenously were also identified. These iatrogenic errors resulted from underlying confusion by physicians about proper dosing of epinephrine for anaphylaxis. The risk of error was amplified by the need for rapid decisionmaking in critically ill anaphylactic patients. An e-mail survey of local hospitals in southeast Michigan revealed that 6 of 7 hospitals did not stock prefilled intramuscular dose syringes for emergency use in anaphylaxis. At our institution, we have introduced prefilled and appropriately labeled intramuscularly dosed epinephrine syringes in crash carts, which are easily distinguished from intravenously dosed epinephrine syringes. In this Concepts article, we describe the clinical problem of inadvertent epinephrine overdose and propose a potential solution. Epinephrine must be clearly packaged and labeled to avoid inappropriate usage and unnecessary, potentially lethal complications in patients with anaphylaxis. [Ann Emerg Med. 2010;55:341-344.]

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INTRODUCTION

Epinephrine is a catecholamine administered for life-threatening conditions of anaphylaxis and cardiac arrest. It is available in different doses and concentrations, to be delivered by various routes for appropriate indications (Table). Intramuscular (IM) dose of 0.3 to 0.5 mg (1:1,000) is recommended for use in anaphylaxis, whereas 0.1 mg (1:10,000) intravenous (IV) epinephrine injected slowly during 5 minutes is reserved for anaphylaxis symptoms refractory to IM doses or anaphylactic shock.¹ This is significantly lower than the dose recommended for cardiac arrest, in which the recommended first dose is a 1-mg (1:10,000) IV push.² Confusion concerning proper dosing and concentrations for different indications has been reported.³⁻¹² Also, epinephrine is available in differing concentrations (1:1,000 and 1:10,000) in multidose vials, which can create another source of drug errors. Numerous case reports of inadvertent epinephrine overdose causing coronary dissection and infarction, cardiomyopathy, transient left ventricular dysfunction, and ventricular arrhythmias have been reported worldwide.³⁻¹¹ During a 5-year period at our hospital, there have been 4 cases of patients

developing serious cardiovascular complications from accidental epinephrine overdose, caused by confusion over appropriate dose and route.

In this Concepts article, our objective is to present 4 cases of potentially lethal complications resulting from inappropriate epinephrine dosing and then to discuss potential causes of this possibly underreported error and present solutions to eliminate this error.

Drug Error Scenarios

Patient 1. A 23-year-old woman with history of asthma was admitted to our hospital for respiratory distress triggered by ingestion of seafood. On presentation, she was found to be tachypneic at 22 breaths/min, with mild inspiratory stridor. She was treated for possible seafood allergy with inhaled racemic epinephrine, IV antihistamines, and corticosteroids, with no improvement of symptoms. During the next few hours, she developed another episode of acute respiratory distress, this time unprovoked by seafood ingestion. Her physical examination was again unremarkable except for inspiratory stridor. Because her working diagnosis at the time was "possible anaphylaxis," a decision was made to administer epinephrine. However, she was

Table. Appropriate epinephrine dose and route for different indications.

Indication	Appropriate Epinephrine Dose per American Heart Association Guidelines
Anaphylaxis	0.3-0.5 mg of 1:1,000 concentration IM
Anaphylactic shock	0.1 mg of 1:10,000 concentration slow IV during 5 min
Cardiac arrest	1 mg of 1:10,000 concentration IV push

erroneously given 2 doses of 1 mg (1:10,000) epinephrine IV push per physician-written order. Subsequently, she developed cardiogenic shock with severe left ventricular dysfunction (ejection fraction of 15%). She was treated with intubation and ventilator support, along with diuretics, after which she had rapid clinical improvement. Repeated echocardiograms after 4 days showed normal ventricular function, with ejection fraction of 60%, confirming our diagnosis of reversible catecholamine cardiomyopathy from epinephrine overdose. Further evaluation revealed paradoxical vocal cord dysfunction as the cause of her stridor and respiratory events.

Patient 2. A 52-year-old woman was admitted to the emergency department (ED) for shortness of breath and throat constriction after ingestion of catfish. Her physical examination was consistent with angioedema, and given her respiratory distress, a decision was made to administer epinephrine. A 0.3-mg 1:1,000 concentration dose was ordered, but the route was not specified in the written order by the physician. The nurse drew the ordered dose from a multidose vial and delivered it IV. Minutes later, the patient developed severe left-sided chest pain, with new-onset ST elevations in leads II, III, and aVF. Her symptoms resolved after 2 doses of 0.4 mg sublingual nitroglycerine and 4 mg IV morphine, with return of ST elevations to baseline. The patient underwent cardiac catheterization, which did not reveal significant coronary artery disease.

Patient 3. A 33-year-old woman was admitted for observation for suspected anaphylaxis to IV iron sulfate. She was hemodynamically stable but had noticeable throat angioedema, as evidenced by tongue swelling. She was erroneously given 0.3 mg (1:1000) IV epinephrine by the nurse, instead of the requested IM injection. Subsequent to this, she developed severe chest pain and ST elevations in her II, III, and aVF leads. Because she continued to complain of chest pain despite 3 mg of IV morphine and 2 doses of 0.4 mg sublingual nitroglycerine, she was taken for an emergency cardiac catheterization, which revealed right-sided coronary artery dissection. She underwent stenting of the vessel, with uneventful recovery.

Patient 4. A 34-year-old man presented with anaphylaxis after ingestion of seafood. His presenting blood pressure was 90/60 mm Hg, and he was tachypneic (26 beats/min), tachycardic (104 beats/min), and in acute distress. IV epinephrine was considered appropriately, but instead of the anaphylactic dose of 0.1 mg (1:10,000) slow IV, he was given the cardiac arrest dose of 1 mg (1:10,000) IV push. Apparently,

there was confusion between the verbal and written order for the drug by the physician per nursing notes. He subsequently became symptomatic, with dizziness and worsening hypotension. Telemetry revealed sustained ventricular tachycardia, which resolved spontaneously. He was observed in the ICU, with no recurrent arrhythmia. Echocardiogram and stress test results were unremarkable.

Problem Evaluation

To determine the total number of admissions for this diagnosis during a 5-year period (2002 to 2007), we extracted the International Statistical Classification of Diseases and Related Health Problems codes for anaphylaxis syndromes and angioedema (995.0, 995.1, 995.6, and 999.4) from our hospital admission database. There were 166 admissions through our ED for anaphylaxis or angioedema, of which we have presented complications in 4 patients (incidence of 2.4%). These 4 patients' cases were presented in our cardiology morbidity and mortality conferences during the 5-year period. We also conducted an informal inpatient pharmacy survey by sending out e-mails to 15 neighboring hospitals in southeast Michigan, with an inquiry about the method of stocking epinephrine in hospital crash carts. Of the 7 hospitals that responded to our survey, only 1 hospital carried prefilled syringes for IM administration in their crash carts. All hospitals had the 1-mg (1:10,000 concentration) IV dose syringe, appropriate for use in cardiac arrest, readily available. The review of collected data and patient information for this report was approved by St. John Hospital and Medical Center Investigational Review Board.

DISCUSSION

Of the 166 patients admitted through our ED with the diagnosis of anaphylaxis during 5 years (2002 to 2007), we report a 2.4% incidence of potentially life-threatening complications from inappropriate epinephrine administration for anaphylaxis. Because these patients are critically ill at arrival to the ED and the effects from IV epinephrine are transient and variable, decompensation caused by epinephrine overdose may go unrecognized. In this Concepts article, we have described 4 errors relating to epinephrine dosing that were presented in our cardiology morbidity and mortality conference during 5 years. Contributions to these errors were multifactorial and included inadequate physician knowledge about appropriate dose and route of epinephrine in anaphylaxis, lack of IM doses in emergency crash carts, complicated dose calculations involving decimals and ratios, and lack of adequate communication between physicians and nurses. Although we did not perform a detailed chart analysis of the other 162 of 166 patients admitted from the ED with anaphylaxis, our numbers may be an underestimation of this iatrogenic error.

Of the 15 hospitals to which we sent out our inpatient pharmacy survey, all 7 responding hospitals had prefilled syringes for IV administration of epinephrine, with doses appropriate for

treatment of cardiac arrest. However, only 1 of the 7 hospitals also carried prefilled syringes for IM administration, as is appropriate for anaphylaxis. Although this survey was not meant to be a rigorous investigation, it does highlight that the potential for errors is not only at our institution.

Patients presenting to EDs with anaphylaxis are very ill and receive multiple, intense therapies. Cardiac arrests require IV epinephrine and account for more in-hospital emergencies than anaphylaxis, which requires IM doses. Therefore, physicians may be more accustomed to giving epinephrine IV than IM.

Epinephrine is available in differing concentrations (1:1,000 and 1:10,000) in multidose vials, which demands a clear understanding of dosage regimen for appropriate drug delivery. This concentration represents the amount of solution in milliliters used to dilute 1,000 mg of epinephrine. For example, a solution labeled as 1:10,000 concentration represents 1,000 mg/10,000 mL, or 0.1 mg/mL. Most hospital emergency crash carts have the solution available only in IV form in doses appropriate for cardiac arrest. General hospital floor medications usually include epinephrine in concentrated, multidose vials to be diluted by the pharmacists to appropriate concentrations for IM use, along with prefilled cardiac arrest IV dose syringes. Physicians may decide to use prefilled, fixed-dose IV syringes of epinephrine in urgent situations, rather than wait for the pharmacists to measure out the IM dose from a vial.

Confusion concerning the differing concentrations of epinephrine preparations is not rare (between 1 mg of 1:10,000 concentration, 0.1 mg of 1:10,000 concentration, and 0.3 to 0.5 mg of 1:1,000 concentration). Rolfe and Harper¹² surveyed 150 teaching hospitals in Great Britain and found that more than 40% of physicians were unable to convert drug doses correctly from percentage concentrations to more conventional mass concentrations. Lesar et al¹³ studied factors related to errors in medication prescribing. They found that gaps in knowledge of a drug, application of the knowledge to a particular situation, and need for calculations using decimal points accounted for 59% of prescription errors.

All of these factors are in play when epinephrine is prescribed urgently for anaphylaxis. Concern about accidental drug overdose was emphasized recently when the Pennsylvania Patient Safety Authority issued a high drug alert about the risk of epinephrine overdose.¹⁴ They recommended that hospitals store a single concentration of drug whenever possible and affix warning labels as appropriate to minimize confusion between the 2 concentrations of epinephrine. Wheeler et al¹⁵ recently published a randomized classroom simulation of 28 physicians that predicted frequent excess epinephrine dosage in clinical practice. Physicians using ampules labeled only with epinephrine ratios (1:1,000 and 1:10,000) more frequently administered excessive epinephrine doses than those using ampules with mass concentration labels ($P=.003$). A recently published survey assessed the knowledge of 253 radiologists across 26 Canadian hospitals for use of epinephrine in management of patients with severe contrast-induced allergic reaction.¹⁶ Not only was no radiologist able to give the ideal

response but also 17% ($n=39$; 95% confidence interval 12% to 22%) of them provided an overdose. Only 11% (27 of 253; 95% confidence interval 7% to 15%) of radiologists knew what concentration of epinephrine was available in their drug kit or crash cart.

Many of the emergency medications, including epinephrine, are available with concentration doses expressed in ratios or percentages. Because they date back to the 1938 Food, Drug and Cosmetic Act, they are considered as United States Pharmacopeia drugs and do not fall under current Food and Drug Administration labeling standards. Until the United States Pharmacopeia eliminates the use of ratio expressions on epinephrine labels, hospitals are encouraged to derive strategies to improve the safe use of epinephrine.

Potential Solutions

At our hospital, a team consisting of residents, fellows, a cardiologist, and an emergency physician discussed potential solutions for the problem with our pharmacy department. We believe that physicians' lack of awareness of appropriate doses and routes for epinephrine use plays a significant role in causing this error. This is made worse by the availability of only IV epinephrine in hospital crash carts. Until the United States Pharmacopeia eliminates the use of dose ratios and presents a simplified and precise labeling method for different formulations, appropriate education and reminders are imperative for the hospital staff. At our hospital, we conducted multiple teaching sessions stressing the use of IM dose of epinephrine instead of IV formulations, as is recommended by the American Heart Association guidelines for anaphylaxis, for residents and faculty members. We now stock IM epinephrine autoinjectors in our emergency carts in prefilled syringes with dosage appropriate for anaphylaxis. These contain 0.3 mg of 1:1,000 epinephrine to be delivered IM and are clearly labeled "Use only for anaphylaxis," with a color code different from that for IV epinephrine. Providing these specifically labeled epinephrine autoinjectors for anaphylaxis may compel the physicians to use the IM route first, as indicated. IV epinephrine containing 1 mg of 1:10,000 concentration is available as a prefilled syringe labeled "Use only for cardiac arrest" (Figure). Multidose vials for IM use have been removed from the emergency carts, though they continue to be available for IV use in anaphylactic shock. We sent memoranda to our staff and to the hospitals in our region we surveyed detailing the potential for inappropriate administration of epinephrine and the changes adopted to avoid the problem. Since the introduction of these measures 2 years ago, there have been no further reported adverse outcomes related to epinephrine overdose identified by our institution's error reporting system. Because this is a rarely reported error, the effect of our endeavors on assessing outcomes is limited. We realize that although the hospital policy changes we made seem to have decreased complications, this is only one process improvement. Other efforts must include increasing awareness and education of nurses and physicians to this



Figure. Clearly labeled prefilled syringes containing (upper box) 0.3 mg of 1:10,000 concentration IM dose in an autoinjector labeled “for anaphylaxis use only.” Lower box contains 1 mg of 1:10,000 concentration IV dose labeled “for cardiac arrest use only.”

problem, increased pharmacist availability, and universalizing epinephrine dosing guidelines.

CONCLUSION

Despite the many observations and alerts about the risk of iatrogenic epinephrine dosing errors, many hospitals remain at risk. We suggest that epinephrine be stocked in prefilled, clearly labeled syringes to prevent these errors.

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