Inadvertent IV Administration of IM Epinephrine

A 2-year-old is treated in the ED for anaphylaxis, but she receives a dose of epinephrine intravenously when it should have been given intramuscularly. Unfortunately, this occurrence is not unique, and it can result in life-threatening complications. The authors discuss important considerations in epinephrine administration and provide details of this and other cases in which misadministration has occurred.

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Case

A 2-year-old girl is brought to the ED via ambulance with difficulty breathing and hives after eating a cashew. She has a history of mild, intermittent asthma. En route, she vomits once and has a near-syncopal episode. Upon arrival at the ED, she is in acute respiratory distress, with wheezing, stridor, and tachypnea (respiratory rate, 40 breaths/min). An urticarial rash is noted. Her other vital signs include a heart rate of 130 beats/min; blood pressure, 90/62 mm Hg; temperature, 37.2°C; oxygen saturation, 98% on face mask oxygen.

Epinephrine (1:1,000 concentration) 0.15 mg is prepared for intramuscular administration for treatment of anaphylaxis. However, the epinephrine is inadvertently administered intravenously. The patient subsequently develops tachycardia (heart rate, 180 beats/min) and hypertension (blood pressure, 120/70 mm Hg).

What is the mechanism of action of epinephrine?

Epinephrine, or adrenaline, is a catecholamine that is produced endogenously in the adrenal medulla. As a medication, epinephrine is administered parenterally as treatment for anaphylaxis and cardiac arrest. Its clinical utility is based on its activity at α- and β-adrenergic receptors. α_1-Adrenergic agonism in the peripheral vasculature results in vasoconstriction. Stimulation of β_1-receptors in the myocardium increases chronotropy and inotropy, leading to increased heart rate and contractility, respectively. Stimulation of β_2-receptors induces smooth muscle relaxation, which in the bronchioles causes bronchodilation. This forms the basis for the use of nebulized or aerosolized epinephrine as treatment for bronchoconstriction. In the peripheral vasculature, β_2-receptor stimulation causes a mild vasodilation that is typically overcome by the vasoconstrictive actions of α_1-adrenergic agonism. The simultaneous vasoconstrictive and bronchodilating effects of epinephrine make it an effective treatment for anaphylactic shock.

How is epinephrine dosing calculated?

Injectable epinephrine is available in two concentrations: 1:1,000 for intramuscular use and 1:10,000 for intravenous use. Epinephrine's antiquated labeling is unusual—it expresses the concentration of the drug in the unconventional ratio format of parts per 1,000 (in this case, 1 gram per 1,000 milliliters, or 1 mg/mL) instead of as the more conventional, but still complicated, percentage concentration (grams per 100 milliliters). Epinephrine is not subject to current FDA labeling requirements because it was in use prior to the enactment of the 1938 Food, Drug and Cosmetic Act.[1] Thus, the formulation intended for intramuscular use (1 mg/mL) is 10 times as concentrated as that intended for intravenous administration (0.1 mg/mL). For this reason it is best to plainly spell out on the label the exact amount, in conventional units (such as mg/mL), that is present in the solution.

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TABLE. Epinephrine Dosing

Indication	Dose
Anaphylaxis	*IM* Adults: 0.3 to 0.5 mg (1:1,000) in thigh Children: 0.01 mg/kg (1:1,000) in thigh (up to 0.3 mg if not using autoinjector) *Prefilled IM autoinjectors* Adults: 0.3 mg (1:1,000) in thigh Children: 0.15 mg (1:1,000 or 1:2,000) in thigh
Anaphylactic shock (refractory)	Adults: 0.1 mg (1:10,000) IV over 5 min Children: 0.01 mg/kg (1:10,000) IV over 5 min (up to 0.1 mg)
Cardiac arrest	Adults: 1 mg (1:10,000) IV push Children: 0.01 mg/kg (1:10,000) IV push

Adapted from American Heart Association[2]; Lieberman et al[3]; Dey[6]; Shionogi[7]; Neumar et al[8]; Kleinman et al.[9]

What are the indications and recommended doses for epinephrine administration?

According to guidelines from the American Heart Association[2] and a joint task force practice parameter published in the *Journal of Allergy and Clinical Immunology*,[3] anaphylaxis should be treated with epinephrine (1:1,000) at a dose of 0.3 to 0.5 mg IM in an adult (0.3 to 0.5 mL) and 0.01 mg/kg IM (up to 0.3 mg) in a child. This dosing can be repeated every 5 to 10 minutes until clinical improvement is demonstrated.[3] Subcutaneous epinephrine administration is no longer recommended because more rapid peak plasma concentrations are achieved when the drug is administered intramuscularly in the thigh.[3-5] Epinephrine is available in prefilled autoinjectors that are designed to deliver 0.3 mg (for adults) or 0.15 mg (for children weighing 15 to 30 kg) of the drug into the thigh.[6,7] For patients who do not respond and demonstrate evidence of anaphylactic shock with profound, refractory hypotension and signs of hypoperfusion, epinephrine (1:10,000) may be administered intravenously at a dose of 0.1 mg in adults and 0.01 mg/kg in children (up to the adult dose) via slow infusion over 5 minutes.[2,3] An IV infusion at rates of 1 to 4 µg/min may be initiated in adults to prevent the need for repeat epinephrine injections.[2]

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Many hospital "crash carts" stock epinephrine in the intravenous formulation that is appropriate only for cardiac arrest, causing confusion or delay when a patient with anaphylaxis requires the more concentrated formulation for intramuscular delivery.

During cardiac arrest, epinephrine (1:10,000) is administered via IV bolus at a dose of 1 mg in adults and 0.01 mg/kg in children (up to 1 mg), repeated every 3 to 5 minutes.[2,8,9] These recommendations are summarized in the Table.[2,3,6-9]

What factors contribute to dosing or other errors with epinephrine administration?

Confusion is common regarding the appropriate dose, formulation, and route of administration of epinephrine. Many hospital "crash carts" stock epinephrine in the intravenous formulation that is appropriate only for cardiac arrest, causing confusion or delay when a patient with anaphylaxis requires the more concentrated formulation for intramuscular delivery. Furthermore, many physicians understandably have difficulty with complex dose calculations and conversions, and this may be magnified under stressful conditions. In a survey of 150 hospital physicians, half were unable to correctly convert doses of epinephrine from a dilution to mass concentration.[10] Physicians may not have adequate insight into the appropriate dose and concentration for anaphylaxis. In another survey of 253 radiologists in 26 US and Canadian hospitals, no physician was able to give the correct dose, concentration, and route of epinephrine administration. Of those surveyed, 17% would have administered an epinephrine overdose.[11]

Inappropriate route of administration (intravenous vs intramuscular) can occur when there is miscommunication between team members caring for a critically ill patient. A retrospective review of patients admitted with anaphylaxis at a single institution over a 5-year period identified a 2.4% incidence of potentially life-threatening complications from inappropriate epinephrine administration.[1] Two of the reported cases involved the inadvertent intravenous administration of a dose and concentration of epinephrine intended for intramuscular use. The causes of these errors were multifactorial and were attributed to inadequate physician knowledge, lack of intramuscular doses in emergency crash carts, complicated dose calculations involving ratios and decimal points, and lack of adequate communication between physicians and nurses. In a survey of inpatient pharmacies, only one of seven responding hospitals had epinephrine available in prefilled syringes for intramuscular administration, as is appropriate for anaphylaxis.[1] Inappropriate intravenous epinephrine administration can also occur with infusion pump malfunction in the setting of continuous infusion.[12]

What adverse effects are associated with inadvertent overdose of epinephrine?

Tachycardia and hypertension occur following intravenous administration of inappropriately high doses of epinephrine. In many patients with acute exposures, these effects can resolve spontaneously without evidence of end-organ effects. Epinephrine is rapidly metabolized and has a short half-life (approximately 2 minutes). However, prolonged cardiovascular toxicity has been described in both adult and pediatric populations, especially when exposure is prolonged by continuous infusion.

Previously Reported Cases

A 23-year-old woman presented with anaphylaxis and was erroneously given two doses of epinephrine 1 mg (1:10,000) as an IV bolus instead of by slow infusion. She developed cardiogenic shock with severe left ventricular dysfunction (ejection fraction of 15%) and pulmonary edema requiring intubation. She returned to normal cardiac function after 4 days.[1]

A 33-year-old woman was erroneously given epinephrine 0.3 mg (1:1,000) IV instead of IM. She subsequently developed a right coronary artery dissection that required intracoronary stenting.[1]

A 5-year-old boy developed acute myocardial ischemia, as evidenced by elevated cardiac enzyme levels, ECG changes, decreased left ventricular systolic function, and pulmonary edema, after he was erroneously given epinephrine intravenously instead of subcutaneously.[13] Ventricular dysrhythmias in children receiving excessive doses of subcutaneous epinephrine as treatment for asthma have been described.[14]

An 18-year-old man receiving continuous epinephrine infusion for septic shock developed tachycardia (heart rate, 198 beats/min), hypertension (blood pressure, 250/188 mm Hg), pulmonary edema, and myocardial damage as evidenced by ECG changes and elevated cardiac enzyme levels. It appears that electromagnetic interference from a nearby cell phone caused a malfunction of the infusion pump, resulting in the delivery of 10.5 mg of epinephrine over a period of 1.4 minutes.[12]

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In one case, it appears that electromagnetic interference from a nearby cell phone caused a malfunction of the infusion pump, resulting in the delivery of 10.5 mg of epinephrine over a period of 1.4 minutes.

What are the therapeutic considerations for iatrogenic epinephrine overdose?

Management priorities in patients with an epinephrine overdose, as with all critically ill patients, are control of airway, breathing, and circulation. Continuous cardiac monitoring and frequent blood pressure measurements should be instituted. ECG should be performed to identify myocardial ischemia. For patients with evidence of myocardial ischemia, end-organ hypoperfusion, cardiac failure, pulmonary edema, or persistent severe hypertension or tachycardia, administration of an antidote should be considered. Phentolamine, a nonselective α-antagonist, can be administered intravenously at doses of 5 mg for adults and 1 mg for children to reverse peripheral and coronary artery vasoconstriction. A short-acting cardioselective β_1-adrenergic antagonist such as esmolol may be considered for refractory tachycardia, though this should be rarely needed. β-Blockade should be avoided without the concomitant administration of phentolamine or another vasodilator to avoid the dangers of unopposed α-adrenergic agonism.

Case Conclusion

An ECG shows sinus tachycardia with normal intervals without evidence of ischemia. Throughout this time, the patient receives intravenous diphenhydramine and methylprednisolone as secondary treatment for anaphylaxis, along with normal saline. Her stridor and respiratory distress improve rapidly, and over a 4-hour observation period her tachycardia and hypertension resolve. She is admitted for overnight observation and is discharged the following day without sequelae. □

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