

A REVIEW OF EPINEPHRINE ADMINISTRATION IN PEDIATRIC ANAPHYLAXIS

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Epinephrine is a high-risk medication that has the potential to save lives. However, in stress-filled and high-acuity environments like the emergency department, there is a greater risk for error with epinephrine. Children are further at risk from errors in weight-based calculations and confusion over drug concentration expression. When administered incorrectly, epinephrine has the potential for significant harm. This review of the literature examines the use of epinephrine in the treatment of pediatric anaphylaxis and discusses commonly identified issues associated with its administration.

Epinephrine

Epinephrine is an α - and β -adrenergic agonist that promotes vasoconstriction, increases blood pressure, decreases capillary leakage, increases chronotropy and inotropy, and promotes bronchodilation.¹ It is used in a variety of pediatric emergency situations, including cardiac resuscitation, asthma exacerbations, croup, and anaphylaxis. Epinephrine comes standard in two forms, 1:1,000 and 1:10,000 solutions. The dose recommended by the American Heart Association for use in pediatric cardiopulmonary resuscitation is 0.01 mg/kg (0.1 mL/kg) of 1:10,000 epinephrine with a maximum of 1 mg administered intravenously and may be repeated every 3 to 5 minutes.² The dose recommended for pediatric anaphylaxis is 0.01 mg/kg (0.01 mL/kg) of 1:1,000 epinephrine with a maximum of 0.3 mg administered intramuscularly to the outer thigh and may be repeated every 5 to 15 minutes for persistent or recurrent symptoms.¹

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Anaphylaxis

The Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium defined anaphylaxis as "a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance."³ At the symposium, clinical criteria were selected to aid emergency personnel in the diagnosis and treatment of anaphylaxis in a consistent and precise manner (Table 1). In a case study of children, food allergy was found to be the major identifiable trigger, accounting for 34% to 57% of anaphylactic reactions. The most common causes of anaphylaxis in non-hospitalized children were food and insect venom, and the most common causes of anaphylaxis in hospitalized patients were drug or latex exposures.⁴ It is estimated that anaphylactic food allergies are responsible for 30,000 ED visits and cause 150 to 200 deaths per year in the United States.⁵

Methods

A thorough review of the literature was performed on epinephrine administration from an online database (PubMed) using keyword search for the following terms: epinephrine, pediatric anaphylaxis, allergic reaction, and epinephrine auto-injector. Current research data were collected from 41 articles and publications. Literature was chosen for review based on pediatric relevance and modern practice standards.

Review of Literature

DRUG CONCENTRATION EXPRESSION

Wheeler et al⁶ evaluated the impact of ampule labeling on physicians' clinical performance in a simulated critical environment and found that physicians are more likely to give the wrong dose of epinephrine and take longer to administer the dose when the strength of epinephrine is expressed in a ratio. Over two-thirds of doctors surveyed said that they would prefer ampules to be labeled with the mass concentration rather than the dilution concentration.⁷

Epinephrine dates back to before the 1938 Food, Drug, and Cosmetic Act and therefore does not fall under current Food and Drug Administration labeling standards. The Pennsylvania Patient Safety Authority advocates that the US Phar-

TABLE 1

Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with the involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus, flushing, or swollen lips/tongue/uvula) and at least 1 of the following:
 - A. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, or hypoxemia)
 - B. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, or incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - A. Involvement of skin/mucosal tissue (eg, generalized hives, itch/flush, or swollen lips/tongue/uvula)
 - B. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, or hypoxemia)
 - C. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, or incontinence)
 - D. Persistent gastrointestinal symptoms (eg, cramping abdominal pain or vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours), with low systolic BP (age specific) or greater than 30% decrease in systolic BP* in an infant or child and systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline in an adult

PEF, Peak expiratory flow; BP, blood pressure.

*Low systemic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than $(70 \text{ mm Hg} + [2 \times \text{age}])$ from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Data from Sampson et al.³

macopeia should eliminate the use of ratio expressions on epinephrine labels. Until this happens, it advises health professionals to use additional safety strategies to prevent errors associated with epinephrine administration⁸ (Table 2).

In response to these data, 1 hospital has chosen to stock epinephrine auto-injectors in its emergency department.⁹ These devices are clearly marked with labels stating "Use only for anaphylaxis" and with a color code different from the intravenous form of epinephrine. The 1:10,000 concentration of epinephrine is also clearly labeled as "Use only for cardiac arrest." Since the introduction of these measures, no further reports of epinephrine overdose have been reported at that institution.⁹

TABLE 2

Safe practice strategies for preventing errors with epinephrine

1. Do not expect all health care practitioners to be familiar with percent or ratio expressions of concentrations or to be adept at calculating doses for drugs with concentrations expressed in this manner.
2. Use prefilled syringes and limit storage of concentrated epinephrine to crash carts (except in the ED and OR) to reduce the risk of dilution errors or administration of the wrong product.
3. Store a single concentration and affix warning labels as appropriate to minimize the confusion between the 2 concentrations of epinephrine.
4. Remember that 1:1,000 epinephrine in 30-mL vials for systemic use presents a hazard and, at least in nurseries, should not be available on units.
5. Post a dose conversion chart reflecting available concentrations on emergency carts and in other areas where this medication may be prepared.
6. During annual CPR certification for clinical staff, review the dose chart and mention potential confusion with drugs dosed in ratio concentration.
7. To ensure an independent double-check system, have pharmacy prepare all infusions and bolus doses for epinephrine.

ED, Emergency department; OR, operating room; CPR, cardiopulmonary resuscitation. Data adapted from Pennsylvania Patient Safety Advisory.⁸

STRESS AND HUMAN ERROR

Human factors play a large role in the occurrence of adverse medication events. Wilson et al¹⁰ report that the intensity of care can greatly influence a patient's risk for injury. One survey of 293 nurses shows that hospital units reporting higher levels of stress among their nurses were routinely more predisposed to exhibit increased patient safety incidents and medication errors.¹¹ Distraction also plays a large role in medication errors. It has been documented that nurses are interrupted at least 10 times an hour, or every 6 minutes, which can increase the potential for error.¹² In 1 study of epinephrine administration, parents were instructed to draw up the medication using an ampule/needle/syringe method and evaluated for time and efficacy. Parents took a significantly longer time drawing up the medication than health professionals, and a much wider range of medication content was aspirated. Use of this method for home administration was deemed impractical, with risk for

overdose, suboptimal dosing, and significantly delayed administration.¹³

UNINTENTIONAL EPINEPHRINE OVERDOSE

Cardiac dysrhythmias and other adverse drug effects have been documented in children receiving an unintentional epinephrine overdose. In the few published cases of pediatric overdose, chest tightness, shortness of breath, palpitations, hemoptysis, tachycardia, ST-segment depression, elevated cardiac enzyme levels, and ischemic changes on electrocardiogram developed in a 14-year-old boy after injection of epinephrine by intravenous push.¹⁴ In another 5-year-old boy, junctional bigeminy, premature ventricular contractions, ST-segment depression, and 2 brief runs of ventricular tachycardia developed after subcutaneous overdose of 1.75 mg of epinephrine.¹⁵ A 14-year-old female was inadvertently given an epinephrine overdose of 5 mg intravenously while in surgery, resulting in sinus tachycardia with T-wave enlargement, followed by an idioventricular rhythm with frequent multifocal premature ventricular contractions, ST-segment depression, and a brief run of supraventricular tachycardia, with eventual return of the heart rate to preoperative levels.¹⁶

ADMINISTRATION ROUTES

Simons et al¹⁷ studied the rate of epinephrine absorption in children and compared the subcutaneous route versus the intramuscular route. The mean maximum plasma epinephrine concentration with subcutaneous drug injection peaked in 34 ± 14 minutes versus 8 ± 2 minutes for the intramuscular route. This study changed the way epinephrine is administered in the pediatric emergency department. Intramuscular injection is currently the standard route of epinephrine administration for acute anaphylaxis.

Studies have been performed to evaluate alternative routes of epinephrine administration for pediatric anaphylaxis. Epinephrine via inhalation in children has been studied, with poor results. Because of the inability of most children to inhale sufficient amounts of epinephrine to increase plasma concentrations, this route is not recommended for the treatment of acute anaphylaxis.¹⁸ Rawas-Qalaji et al¹⁹ performed rabbit studies comparing sublingual epinephrine tablets versus intramuscular injections. Administration of 40-mg rapidly disintegrating sublingual tablets resulted in plasma epinephrine concentrations similar to those obtained after intramuscular injection of 0.34 mg in the thigh.

EPINEPHRINE AUTO-INJECTORS

Auto-injectors were originally developed for military personnel, allowing rapid injection of potentially lifesaving medications in high-stress battlefield situations.²⁰ Cur-

rently, there are 2 fixed doses available on the market for self-injectable epinephrine: 0.15 mg (eg, EpiPen Jr [Dey Pharma, L.P., a subsidiary of Mylan Inc., Napa, CA]) and 0.3 mg (eg, EpiPen [Dey Pharma, L.P.]).²¹ It is vital that patients have their auto-injectors available at all times. In case reports from fatal pediatric anaphylactic reactions, most reactions occurred outside of the home.²² In 1 survey, only 40% of children kept an auto-injector device at school.²³ From a human factors design standpoint, it has been suggested that the creation of smaller pocket-sized devices and keychain attachments could help improve portability.²⁴ In addition, it is necessary for patients to track the expiration date of their auto-injectors because the contents of outdated auto-injectors have been shown to have significantly reduced bioavailability compared with in-date auto-injectors.²⁵ Patients and their families are instructed to arrive at the emergency department after epinephrine auto-injector use because it is common to require multiple doses of epinephrine during anaphylaxis. In a 2010 study, 16% of patients with stinging insect-induced anaphylaxis required a second dose.²⁶ In an earlier, more comprehensive study, more than 35% of patients needed more than 1 dose of epinephrine.²⁷

AUTO-INJECTOR DOSING LIMITATIONS

Because of the limited doses of fixed-dose auto-injectors, providers must determine whether to under-dose or overdose their patients based on the availability of devices. The 2011 *Physicians' Desk Reference* states the following:

Usual epinephrine adult dose for allergic emergencies is 0.3 mg. For pediatric use, the appropriate dosage may be 0.15 or 0.30 mg depending upon the body weight of the patient. A dosage of 0.01 mg/kg body weight is recommended. The EpiPen Jr, which provides a dosage of 0.15 mg, may be more appropriate for patients weighing less than 30 kg. However, the prescribing physician has the option of prescribing more or less than these amounts, based on careful assessment of each individual patient and recognizing the life-threatening nature of the reactions for which this drug is being prescribed. The physician should consider using other forms of injectable epinephrine if doses lower than 0.15 mg are felt to be necessary.²⁸

It has been suggested that several more fixed doses of auto-injectors or a device with an adjustable pharmacy-set dose should be manufactured to avoid these issues in dosing pediatric patients.²⁹ Until a wider range of epinephrine auto-injector doses are available, pediatricians must consider prescribing an auto-injector with a known but not ideal dose.³⁰

UNINTENTIONAL EPINEPHRINE INJECTIONS

Between 1994 and 2007, 15,190 unintentional injections from epinephrine auto-injectors were reported to US Poison

TABLE 3

EpiPen directions for use

1. Remove from the carrier tube by flipping open the yellow (EpiPen) or green (EpiPen Jr) cap and slide the unit out of the carrier tube.
2. Grasp the unit with the orange tip pointing downward.
3. Form your fist around the unit (orange tip down).
4. With your other hand, pull off the blue safety release.
5. Hold the orange tip near the patient's outer thigh. Do not inject into the buttock.
6. Swing and firmly push the unit against the patient's outer thigh until it clicks so that the unit is perpendicular (at a 90° angle) to the thigh. (The auto-injector is designed to work through clothing.)
7. Hold the unit firmly against the patient's thigh for approximately 10 seconds to deliver drug. (The injection is now complete. The window on the auto-injector will be obscured.)
8. Remove the unit from the patient's thigh (the orange needle cover will extend to cover the needle), and massage the injection area for 10 seconds.
9. Call 911 and seek immediate medical attention.
10. Take the used auto-injector with you to the hospital emergency department.

Data adapted from EpiPen patient information.²¹

Control Centers.³¹ A review of these charts showed that the majority of these events caused injury to the finger or thumb and reports of serious or permanent injuries were rare.³¹ Pain, tingling, blanching, and coldness to the digit have been reported with positive reversal of effects with phenolamine injections in a child.³² Phenolamine is a high-risk drug that has been approved for the use of extravasation of drugs that have α -adrenergic effects such as epinephrine.³³ From a human factors design standpoint, it is important to discuss with families that an EpiPen does not actually function like a pen. This metaphor can lead to the tendency to place one's thumb over the top of the device and, if misplaced, could lead to unintentional injection.²⁴

AUTO-INJECTOR NEEDLE LENGTHS

In a study of 256 children, the needle length of the EpiPen and EpiPen Jr was evaluated by use of ultrasound technology to measure the distance from the skin's surface to the fascial layer of the vastus lateralis muscle to determine whether the length of the needle was adequate for intramuscular medication delivery.³⁴ The EpiPen Jr has a needle length of 12.7 mm, and the EpiPen has a needle length of 15.8 mm. During testing of the EpiPen Jr, it was found that 12% of

patients had a skin-to-muscle surface distance of greater than 12.7 mm. During testing of the EpiPen, 30% of children had a skin-to-muscle surface distance of greater than 15.8 mm. Needle length on commercially available auto-injectors was determined to be insufficient to reach the muscle in a significant number of children. Additional pressure is needed to ensure adequate medication delivery to the muscle. Because children tend to inject the device less forcefully, it is recommended that an adult give the injection.³⁵

LACK OF KNOWLEDGE

Results of a survey by Huang³⁶ show that many patients are not properly instructed regarding the use of their prescribed auto-injectors. In another study, only 36% of parents were able to correctly fire the auto-injector device.³⁷ When demonstrating the auto-injector technique, the most frequent error was not holding the device in place for 10 seconds.³⁸ A patient's lack of understanding of auto-injector use may in part be a result of provider confusion regarding its use. Only 21% of physicians were familiar with and able to demonstrate the correct use of such a device.³⁹ In another study only 24% gave written materials regarding indications for use of the device.⁴⁰ In addition, it has been shown that many physicians do not have epinephrine training devices with which to educate their patients.⁴¹ The EpiPen directions for use are listed in Table 3.

Discussion

Epinephrine administration is challenging for health professionals for many reasons. Currently, there is no international standard for the labeling of epinephrine, and it does not fall under the current Food and Drug Administration labeling standards. Ratio-based dosing is confusing for health professionals and should be eliminated by the US Pharmacopeia. Epinephrine labeling should be standardized, and epinephrine should be labeled with mass concentration in milligrams. Epinephrine 1:100 can be used outside of anaphylaxis in pediatric patients. It may be administered via the ET route during a code situation and may be administered subcutaneously as a bronchodilator. If possible, the 2 doses should be stored in separate areas of the department. Intramuscular injection remains the standard route of medication administration for anaphylaxis. Additional research is needed to evaluate the effectiveness of alternative routes of administration in pediatric anaphylaxis.

Healthy work environments are essential for institutions that value safe medication practices. Medication preparation rooms should be well-lit and free from distraction. There should be designated "distraction-free zones" in medication rooms to allow for limited interruption during

preparation. Epinephrine should have mandatory independent 2-provider verification checks before administration. High-risk departments such as the intensive care unit and the emergency department should have a limited nurse-to-patient ratio to minimize the risk of errors associated with medication administration. Patients with symptoms of acute anaphylaxis should be closely monitored, and nursing care should be available on a 1:1 basis until the patient's condition is stabilized.

Available resources and technology should be used to avoid error. Computerized order-entry programs should be programmed with a hard stop for ordered intramuscular doses of 1:1,000 epinephrine greater than 0.3 mg. Pediatric emergency departments should stock user-friendly epinephrine auto-injectors for use during pediatric anaphylaxis instead of ampules of epinephrine because this could greatly decrease the risk for harm associated with overdose. Alternatively, for large institutions, a dedicated 24-hour pharmacist available for preparing high-risk infusions and emergency medications could be used to ensure safe medication constitution and administration.

Challenges remain in optimizing the dosing of epinephrine for children weighing less than 15 kg because the recommended dosing for pediatric anaphylaxis is 0.01 mg/kg. When prescribing the 0.15-mg auto-injector, providers must determine whether the risks from a 3-fold overdose for children weighing 5 kg and a 2-fold overdose for children weighing 7.5 kg outweighs the potential for harm from confusing ratio-based multi-dose ampules. For children weighing greater than 15 kg but less than 30 kg, providers must determine whether under-dosing with the 0.15-mg auto-injector or overdosing with the 0.3-mg auto-injector is more judicious. In addition, implementing auto-injectors in the emergency department may be cost prohibitive because devices such as the EpiPen can cost between \$50 and \$150 depending on subsidy²³ versus the less user-friendly, less-expensive ampule that costs approximately \$1.¹³ The cost of auto-injectors may be cost prohibitive, but it can never outweigh the cost incurred by the hospital of a patient who has received an epinephrine overdose.

Patient and family education is extremely important. Health professionals have shown confusion over epinephrine concentration expression and deficient knowledge of auto-injector use. Health providers must have this knowledge to provide families adequate information and instruction in preparation for future emergencies. Inpatient and outpatient institutions should have auto-injector training devices and written materials available to aid in teaching and demonstration. Dedicated staff members assigned to assist with educating patients and

families regarding auto-injector use could improve outcomes. In addition, institutions should have a clear policy regarding the use of epinephrine auto-injectors, and staff competency should be routinely evaluated in the use of the device.

Conclusion

Epinephrine is an important lifesaving medication that is useful in the treatment of acute anaphylaxis in children. The current labeling standards on ampules increases the risk for errors associated with the administration of this medication. These risks appear to outweigh the benefits for children weighing 15 kg or more. In places like the emergency department where high volume and high acuity can lead to a stressful, error-prone environment, ampule-based administration should be replaced by standardized epinephrine auto-injectors for patients weighing 15 kg or more. Such devices could greatly reduce the risk of cardiac injury or death from epinephrine overdose. However, epinephrine auto-injectors have issues of their own, including dosing dilemmas, usability, and cost-efficiency. Institutions must decide how to best address these issues, with the safety of each patient being the highest of standards. Adequate instruction must be given to families using demonstration with trainer devices, written materials, and frequent reinforcement. A plan of action must be initiated to ensure that medical professionals remain competent in understanding and educating patients on the use of these devices.

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