

Summary and simulation of reported adverse events from epinephrine autoinjectors and a review of the literature

Marcus Shaker, MD, MS^{a,b,c}, Dana Toy, BS^a,
Christopher Lindholm, MD^c, Jeffrey Low, PharmD^{a,b},
Erin Reigh, MD^{a,c}, and
Matthew Greenhawt, MD, MBA, MSc^d



Clinical Implications

- Epinephrine is first-line treatment for anaphylaxis. The Food and Drug Administration reported that adverse events from epinephrine are infrequent. Continued patient education on timing, technique, and route of administration remains a critical component of anaphylaxis management.

TO THE EDITOR:

Anaphylaxis has an estimated lifetime population prevalence of 0.05% to 5%.¹ Epinephrine is the recommended first-line treatment for anaphylaxis and delays in use are associated with fatality from cardiovascular and respiratory compromise.²

In contrast to antihistamines, epinephrine affects multiple physiologic targets, including α -1 and β -1 adrenergic receptors in the heart and vasculature. Because of its superior therapeutic effect, early epinephrine use during anaphylaxis is critical.³ In canine anaphylaxis, when epinephrine administration (intramuscular or intravenous epinephrine [0.01 mg/kg]) was delayed by more than 15 minutes in the setting of profound hypotension, the therapeutic effect was lost.⁴ Despite the importance of early epinephrine use, it remains underused in anaphylaxis. One possible reason for epinephrine avoidance is concern for adverse events.³ The purpose of this study was to review the literature regarding adverse events associated with epinephrine use in the treatment of allergic reactions, summarize adverse events that have been reported to the Food and Drug Administration (FDA), and simulate expected rates of reported adverse events from autoinjectors.

A systematic electronic search of MEDLINE (via PubMed and Ovid) and CINAHL (using EBSCO) was conducted using search terms “epinephrine,” “anaphylaxis,” and “adverse event.” Additional literature was obtained through searches with themes related to epinephrine, anaphylaxis, and adverse events (see Figure E1 in this article’s Online Repository at www.jaci-inpractice.org). We also queried the FDA adverse events reporting system to obtain reports of adverse events associated with epinephrine autoinjectors. Finally, we used a computer simulation (Tree Age Pro, Williamstown, Mass) to estimate the population frequency of anaphylaxis, epinephrine autoinjector use, and the rate of adverse events in the at-risk US population of 326,997,869 persons using Markov modeling (see Figure E2 and Table E1 in this article’s Online Repository at www.jaci-inpractice.org).

Table E2 in this article’s Online Repository at www.jaci-inpractice.org summarizes medical literature related to adverse epinephrine events. These included cases of dosing errors (more common with intravenous than with intramuscular epinephrine use), inadvertent lacerations, accidental digital injection and bone injury, coronary vasospasm, myocardial infarction, and cardiomyopathy. One review of accidental autoinjector use from the National Poison Data System summarized notable patterns of injury.⁵ There were 6806 cases of accidental autoinjector use over the 2-year study period, 41% occurring in children 0 to 5 years old. “Minor” clinical effects were reported in 42% of cases and 7% of patients had no effects from unintentional injection. While a limitation to this report was that 39% of subjects did not have severity outcome data available, only 8% of patients reported moderate effects, and major effects were recorded in only 2 cases. The most common accidental injection site was the digit, thumb, or hand for the EpiPen and EpiPen Jr devices (67% and 63% in these locations) and the leg/thigh for the Auvi-Q device (78% in this location). A common cause of accidental injection was mistakenly using a live device rather than a training device when practicing technique.

Adverse cardiac events from epinephrine use present a diagnostic challenge, and have been reported in patients using beta-blocker medications as well as patients not receiving cardiac medications, and in patients with underlying cardiovascular disease as well as those with normal coronary arteries. Stress (Takotsubo) cardiomyopathy can mimic myocardial infarction and is characterized by ST-segment elevation electrocardiogram changes, serum troponin elevation, and apical hypokinesis on echocardiography in the absence of obstructive coronary artery disease. It occurs predominately in elderly women following an intense emotional or physical trigger and is thought to be due to myocardial stunning in the setting of catecholamine excess.⁶ Several cases of this disorder have been linked to epinephrine administration. Nazir et al⁷ published a systemic review and meta-analysis identifying 41 cases of Takotsubo cardiomyopathy associated with epinephrine use.⁷ While the risk of this condition is greater with intravenous versus intramuscular epinephrine use, it may also occur with intramuscular use in young adults.⁸ In contrast, allergic vasospastic angina (Kounis syndrome) is a rare cardiac manifestation of anaphylaxis in which inflammatory cytokines associated with mast cell activation trigger coronary artery vasospasm and/or plaque rupture.⁹ Although their etiologies differ, additional epinephrine administration must be carefully considered if used in both these conditions. In addition, myocardial infarction has been reported following epinephrine use during anaphylaxis in the setting of underlying coronary artery disease. The degree of relative risk from beta-blocker use and underlying coronary artery disease in regard to epinephrine use during anaphylaxis is unknown because no controlled trials comparing adverse event rates in populations with and without these conditions have been published.

In recent years, adverse epinephrine event reporting to the FDA has increased (primarily EpiPen), but caution is needed when interpreting publicly reported databases because the data lack clinical context (Figure 1). Reasons for the increase in adverse event reporting are not known with certainty. Although

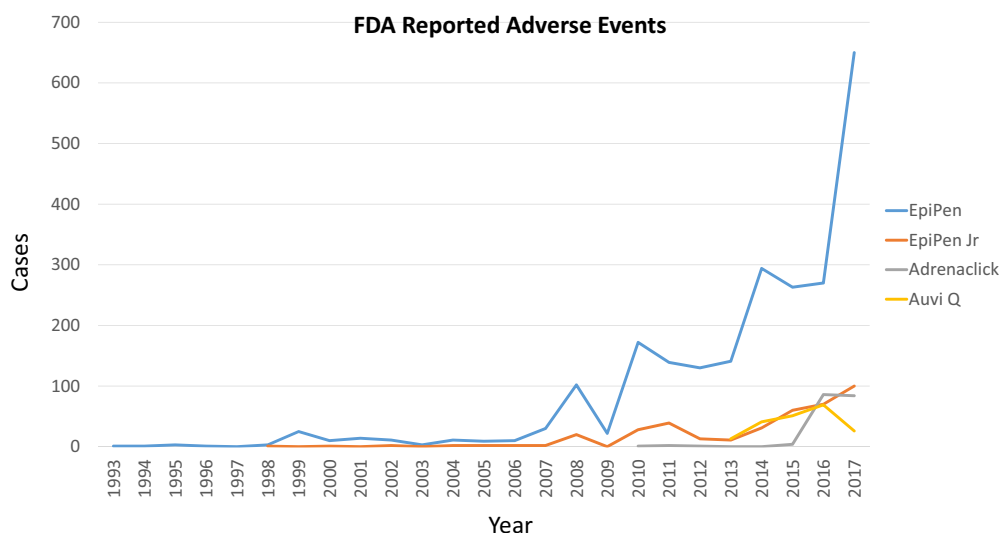


FIGURE 1. FDA-reported adverse events by device and year, 1993-2017.

death has been reported as an adverse epinephrine event (between 1993 and 2017, 101 deaths were reported in association with EpiPen or EpiPen Jr use), it is difficult to differentiate whether these events are due to an actual adverse epinephrine event, delayed administration, device failure, or inability of epinephrine to reverse progressive anaphylactic shock or the underlying condition being treated with epinephrine.

To better estimate the true risk of adverse events, informed by the reported data, we performed a computer simulation of anaphylaxis and epinephrine use across the US population. Our simulation yielded 77,687 epinephrine administrations each year, with a 1.1% rate of FDA-reportable adverse events. Serious adverse events occurred in 0.73% of administrations, with reported epinephrine-associated death in 0.07% of recipients. The overall risk of accidental injection was only 4.3%. Because the simulation was based on FDA reports, limitations of this simulation and review include possible misclassification, and incomplete or inaccurate reports. In the base-case simulation, 226 cases of fatal anaphylaxis occurred each year; however, modeling a 10-fold increased risk of fatal anaphylaxis from epinephrine nonuse resulted in 1090 annual simulated anaphylaxis fatalities.

Our study identified several areas for intervention that may improve the safety of epinephrine administration. First, intravenous epinephrine use during anaphylaxis was associated with a higher rate of adverse cardiac events compared with intramuscular dosing, and should be avoided outside of anaphylaxis refractory to intramuscular epinephrine. Second, providers must be vigilant to avoid dosing errors associated with the lower concentration of epinephrine used in intravenous administration (1:10,000 vs 1:1,000 used intramuscularly). Third, providers should be cognizant of the risk of epinephrine use when patients present with cardiac manifestations, which may include stress cardiomyopathy and allergic vasospastic angina. Fourth, it is important to educate patients and families on proper device use and warn families to make sure they are using a trainer device when practicing, not a live device.

In summary, significant adverse events from epinephrine are infrequent and fear of such events should not prevent rapid epinephrine use during anaphylaxis.

^aGeisel School of Medicine at Dartmouth, Hanover, NH

^bChildren's Hospital at Dartmouth, Lebanon, NH

^cDartmouth-Hitchcock Medical Center, Section of Allergy and Clinical Immunology, Lebanon, NH

^dChildren's Hospital Colorado, University of Colorado School of Medicine, Department of Pediatrics, Section of Allergy and Immunology, Aurora, Colo

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Corresponding author: Marcus Shaker, MD, MS, Section of Allergy and Clinical Immunology, Children's Hospital at Dartmouth, Department of Pediatrics, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756. E-mail: Marcus.shaker@dartmouth.edu.

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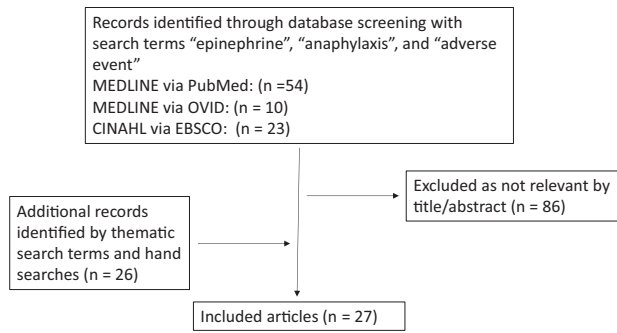


FIGURE E1. Literature review search strategy.

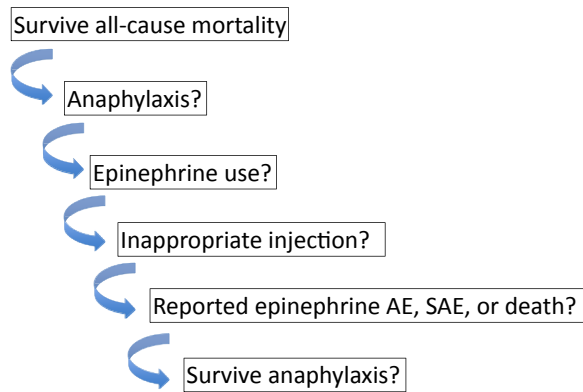


FIGURE E2. Markov transitional health states simulated to evaluate risk of epinephrine autoinjectors. AE, Adverse event; SAE, severe adverse event.

TABLE E1. Simulation inputs and assumptions

Variable	Input	Source
Annual probability of anaphylaxis	42 per 100,000	E1
Probability of fatal anaphylaxis	0.69 per million persons	E2
Adverse epinephrine autoinjector events (annual)	860 cases	E3
Severe adverse epinephrine autoinjector events (annual)	568 cases	E3
Death from epinephrine autoinjectors	54 cases	E3
Accidental injection (annual)	3403	E4
Probability of epinephrine treatment during anaphylaxis	0.57	E5
US population	326,997,869	E6
Life expectancy	2013 US Life Table	E7

TABLE E2. Literature review of adverse events following epinephrine use for anaphylaxis

Title	Year	Comment	Study type	Reference
Epinephrine-induced myocardial infarction in a patient with angiographically normal coronary arteries	1986	Epinephrine given subcutaneously	Case report	E8
Myocardial infarction induced by coronary vasospasm after self-administration of epinephrine	1993	EpiPen self-administered for idiopathic anaphylaxis	Case report	E9
Prehospital epinephrine overdose in a child resulting in ventricular dysrhythmias and myocardial ischemia	1993	Ventricular dysrhythmias and myocardial ischemia in a 5-y-old boy who received 10 times the recommended dose of subcutaneous epinephrine	Case report	E10
Accidental injection of adrenaline in a finger with EpiPen	1998	Accidental injection of 0.3 mg epinephrine in the right pollux	Case report	E11
Lessons for management of anaphylaxis from a study of fatal reactions	2000	Epinephrine overdose caused at least 3 deaths	Registry	E12
Acute myocardial infarction after administration of low-dose intravenous epinephrine for anaphylaxis	2002	Acute myocardial infarction after administration of intravenous epinephrine for anaphylaxis	Case report	E13
Adrenaline given outside the context of life-threatening allergic reactions	2003	Ischemic changes, chest pain, and hypertension following EpiPen administration in a 64-y-old man when treated for angioedema and pulseless ventricular tachycardia in a 40-y-old woman treated for angioedema with intravenous epinephrine	Case series	E14
Management of adrenaline (epinephrine) induced digital ischaemia in children after accidental injection from an EpiPen	2004	Three cases of inadvertent digital EpiPen injection described; phentolamine may be a useful adjunct in treatment if peripheral perfusion is inadequate	Case series	E15
Accidental perforating bone injury using the EpiPen autoinjection device	2005	A perforating injury of the index finger is described	Case report	E16
Postoperative ST-segment elevation: was vasospasm caused by anaphylaxis or by its treatment with epinephrine?	2006	Epinephrine was administered intravenously; Troponin t level was elevated	Case report	E17
Tako-tsubo-like cardiomyopathy after EpiPen administration	2008	EpiPen given for generalized urticaria and angioedema to 76-y-old woman with a history of hypertension treated with β -blocker and coronary artery disease	Case report	E18
Re: spasm of the digital vessels after accidental EpiPen release - a simple solution to a potentially increasing problem	2008	Left thumb was pale, cold, and pulseless on Doppler examination following EpiPen digital injection; perfusion restored within 5 min of phentolamine treatment	Case report	E19
Apical ballooning syndrome after administration of intravenous epinephrine during an anaphylactic reaction	2009	Epinephrine was administered intravenously	Case report	E20
Iatrogenic epinephrine-induced reverse Takotsubo cardiomyopathy: direct evidence supporting the role of catecholamines in the pathophysiology of the "broken heart syndrome"	2009	Epinephrine overdose by intramuscular route in 24-y-old patient with anaphylaxis; patient received 5 mg intramuscularly instead of 0.5 mg	Case report	E21
Voluntarily reported unintentional injections from epinephrine autoinjectors	2010	Review of 15,190 unintentional injections reported to US Poison Control Centers between 1994 and 2007. The number of unintentional injections increased over this period	Observational study	E22
Inverted takotsubo cardiomyopathy secondary to adrenaline injection	2011	Epinephrine administered for presumed anaphylaxis	Case report	E23
Epinephrine-induced myocardial infarction in severe anaphylaxis: is nonselective β -blockade a contributory factor?	2013	Case of propranolol predisposing to ischemic cardiac event following treatment with intramuscular epinephrine	Case report	E24
Cardiac anaphylaxis: a case of acute ST-segment elevation myocardial infarction after IM epinephrine for anaphylactic shock	2013	Acute anterior wall myocardial infarction following intramuscular epinephrine in a 62-y-old man. On percutaneous coronary intervention a thrombus was identified in the mid left anterior descending artery	Case report	E25
Reverse Takotsubo cardiomyopathy in the setting of anaphylaxis treated with high dose intravenous epinephrine	2013	Epinephrine overdose administered intravenously	Case report	E26

(continued)

TABLE E2. (Continued)

Title	Year	Comment	Study type	Reference
Epinephrine in anaphylaxis: higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine	2015	Risk of overdose and adverse cardiovascular events is significantly higher with IV bolus epinephrine compared with intramuscular administration	Observational study	E27
Takotsubo cardiomyopathy caused by epinephrine-treated bee sting anaphylaxis: a case report	2015	Epinephrine was administered intravenously	Case report	E28
Lacerations and embedded needles caused by epinephrine autoinjector use in children	2016	Twenty-two cases of epinephrine autoinjector-related injuries are described	Case report	E29
Unintentional epinephrine auto-injector injuries: a national poison center observational study	2016	A total of 6806 cases of unintentional epinephrine autoinjector exposures were reported to US poison centers in 2013 and 2014	Observational study	E4
Rare case of stress cardiomyopathy due to intramuscular epinephrine administration	2016	Epinephrine was administered intramuscularly for presumed anaphylaxis	Case report	E30
Myocardial infarction during anaphylaxis in a young healthy male with normal coronary arteries—is epinephrine the culprit?	2017	Epinephrine was administered intramuscularly to a 21-y-old man following urticarial rash and difficulty breathing 1 h after ingestion of prawns, a known allergen	Case report	E31
Safety of adrenaline use in anaphylaxis: a multicentre register	2017	In a review of 277 cases, side effects were noted in 21.6% of cases and were usually mild and transient, including tremors, palpitations, and anxiety. Elevated blood pressure, chest discomfort, or electrocardiograph alterations occurred in 3% of subjects	Observational study	E32
Takotsubo cardiomyopathy associated with epinephrine use: a systematic review and meta-analysis	2017	41 cases of Takotsubo cardiomyopathy associated with epinephrine use are described	Meta-analysis	E33

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