

The TEN study: time epinephrine needs to reach muscle

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Background: An epinephrine autoinjector (EAI) is designed to deliver epinephrine into the vastus lateralis muscle. Several studies have demonstrated both patient and physician difficulties in correctly using EAIs, specifically premature removal of the device from the thigh.

Objective: To evaluate the correlation between duration of injection with an EAI and amount of epinephrine absorbed into muscle tissue.

Methods: Twenty-one EAI devices (0.3 mL) were used to determine the amount of epinephrine injected into marbled beef during 7 time periods. A digital scale was used to record preinjection and postinjection weights of EAIs and beef. The weight difference between the preinjection and postinjection periods of the EAIs was used to calculate the total amount of epinephrine released and available for absorption into the marbled beef. The difference between the preinjection and postinjection beef weight was used to determine the amount of epinephrine absorbed into the meat.

Results: The correlation with duration of injection for both the amount of epinephrine absorbed and released was 0.321 ($P = .48$). At all intervals, 95.9% or more of epinephrine was absorbed into the marbled beef. The correlation with duration of injection and percent of epinephrine absorbed was 0.464 ($P = .29$). There were no time periods that were significantly different from the percentage of epinephrine absorbed by the marbled beef at 10 seconds (analysis of variance $P = .16$).

Conclusion: No linear relationship between time and amount of epinephrine injected or absorbed into muscle tissue was demonstrated. These data suggest that holding the device in place for 1 second is as effective as 10 seconds.

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INTRODUCTION

Anaphylaxis is a serious systemic allergic reaction that progresses rapidly and can be fatal when unrecognized or treated inappropriately. Treatment with epinephrine is a lifesaving therapy and should be administered promptly at the onset of apparent anaphylaxis.¹ Patients with venom, food, and latex allergy are often prescribed epinephrine autoinjectors (EAIs) to use in an out-of-hospital setting for treatment of anaphylactic events. Successful treatment of anaphylaxis in an out-of-hospital setting requires several vital steps: (1) availability of self-injectable epinephrine, (2) knowledge of when and how to use the device, and (3) proper administration technique.² Optimal first-aid dosing of epinephrine is defined as 0.01 mg/kg of a 1-mg/mL (1:1,000) formulation to a maximum dose of 0.5 mg in an adult or 0.3 mg in a child.¹ This dosing regimen is based on tradition and clinical consensus

rather than randomized controlled trials.³ Randomized controlled trials examining patients in an anaphylaxis setting would best answer questions regarding optimal dosing of epinephrine and duration one should hold an EAI in place to maximize epinephrine delivery into muscle tissue. However, studies using patients in the midst of a true reaction cannot ethically be performed.

Prefilled EAIs, such as the EpiPen (Dey LP, Napa, California) and TwinJect (Shionogi Pharma, Atlanta, Georgia), are commonly prescribed for out-of-hospital treatment of anaphylaxis. The origin of the EAI dates back to the work of Dr Stanley J. Sarnoff, former chief of the cardiovascular physiology laboratory at the National Institutes of Health and chief executive of the former Survival Technology Inc. During his lifetime, he invented numerous medical devices, notably the autoinjector. Dr Sarnoff's work in the 1950s led to the development of the atropine autoinjector, which was used by military members as an antidote for chemical nerve agent poisoning in the battlefield and which served as the prototype for today's EAI.

The EAI is designed to deliver a single dose of 0.15 mg (pediatric) or 0.3 mg (adult) of epinephrine in a sterile solution into the vastus lateralis muscle. Instructions on proper EAI administration generally include the manufacturers' recommendation to hold the EAI in place for approximately 10 seconds to ensure adequate delivery of the medication. The patient instruction leaflet for the EpiPen states, "Hold firmly against thigh for approximately ten seconds to deliver drug."

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The TwinJect patient instruction leaflet states, “Press down hard until the needle enters your thigh (upper leg) through your skin. Hold it in place while slowly counting to 10.”

Several studies have demonstrated both patient and physician difficulties in correctly using EAI. ⁴⁻⁶ One barrier identified in correctly using EAI is the psychological component of fear and anxiety associated with the use of needles. ^{2,7} In the critical setting of anaphylaxis, this fear and anxiety may jeopardize the patient’s ability to hold the device in place long enough to administer an effective dose of epinephrine. Our study sought to determine the correlation between duration of injection (using an EAI) and amount of epinephrine solution absorbed into muscle tissue.

METHODS

Twenty-one EpiPen devices (0.3 mL) were used to determine the amount of epinephrine solution injected into a section of beef during 7 different injection-duration periods (1, 2, 3, 4, 5, 6, and 10 seconds). Marbleized beef (containing various amounts of intramuscular fat) was used in this study to simulate human muscle tissue. An AG104 Mettler Toledo analytical balance scale (Mettler-Toledo GmbH, Laboratory & Weighing Technologies, Greifensee, Switzerland) with accuracy to 0.0001 g was used to record preinjection and postinjection weights of EAI and beef. The weight difference between the preinjection and postinjection periods was used to calculate the total amount of epinephrine released and available for absorption into the marbleized beef. The marbleized beef was wrapped in moisture-proof Parafilm wrapping before injection. Any epinephrine solution that dripped off the needle onto the Parafilm wrapping when the device was removed was blotted dry with tissue paper before being weighed. This step was done to prevent epinephrine outside the meat from being included in the postinjection (total amount of epinephrine absorbed) weight. The difference between the preinjection and postinjection beef weight was used to determine the amount of epinephrine absorbed into the meat. Calculated values of epinephrine released or absorbed that exceeded 0.30 mg were not truncated at 0.30 mg so that variability would not be artificially reduced. All weighing of pens and beef were made 3 times and the results averaged. The amount absorbed was then divided by the amount released to determine the percentage of absorption for each EAI trial. Three trials were conducted with three separate EAI at each period, and the percentage of absorption was averaged to account for variability between trials. Coefficients of variation were determined for the average percentage of absorption at each period. If the coefficient of variation exceeded 5%, the trial for the entire period was repeated. To minimize operator variability, 2 separate single investigators (T.B., E.R.) timed the experiments and operated the EAI. The percentage of absorption was compared across the 7 injection-duration periods with 1-way analysis of variance (ANOVA). In addition, Spearman rank correlation coefficients were determined to test for linear relationships between

injection-duration period and amount of epinephrine injected and absorbed and the percentage absorbed.

The pressure within the marbleized beef wrapped in Parafilm was determined using a Stryker handheld pressure monitoring device (Stryker, Kalamazoo, Michigan). This device was primed with saline and zeroed while held in the position in which it would be used. The needle was then inserted into the beef and 0.3 mL of saline was injected. Three pressures were recorded and averaged.

RESULTS

The results from the 7 time periods are depicted in Figure 1. The average amount of epinephrine released ranged from 0.284 to 0.304 mL, and the average amount absorbed ranged from 0.274 to 0.308 mL. The correlation between the duration the EAI was held in place and the amount of epinephrine absorbed and amount released was coincidentally the same at 0.321 ($P = .48$). At all intervals, 95.9% or more of epinephrine released from the EAI was absorbed into the marbleized beef, with calculated values ranging from 95.9% to 101.4%. The coefficient of variation ranged from 1.1% to 3.1% across the trials. The correlation between duration the EAI was held in place and percent of epinephrine absorbed was 0.464 ($P = .29$). There were no periods that were significantly different from the percentage of epinephrine absorbed by the marbleized beef at 10 seconds (ANOVA P value = .16). The 3 pressures measured using the Stryker handheld device were averaged and noted to be 14.6 mm Hg.

DISCUSSION

The frequency of anaphylaxis, determined by EAI prescriptions, has been estimated to be approximately 50 to 2,000 episodes per 100,000 persons or a lifetime prevalence of 0.05% to 2.0%. ⁸ Outpatient management of individuals at risk for anaphylaxis should include providing these patients with an EAI and training on how to use the device, a written personalized anaphylaxis action plan, and instructions on how to obtain a medical identification bracelet or necklace. ⁹ Studies have clearly demonstrated that both patients and physicians commonly make errors when using EAI training devices. ⁴⁻⁶ Common barriers of using an EAI correctly include prematurely removing the EAI from the thigh, not removing the cap to activate the device, self-injecting the device into the thumb, and injecting at an incorrect site (ie, hip, arm, stomach). These studies all demonstrated that injecting and quickly removing the EAI instead of holding it in place for the correct time was one of the most frequent mistakes made by patients and physicians. In the critical nature of an anaphylactic event, factors such as heightened anxiety, pain, or fear of the needle may contribute to patients prematurely removing the device. ⁷

Intramuscular injection of epinephrine into the thigh has been demonstrated to be the superior method of administration. ¹⁰ Prematurely removing an EAI from the thigh raises a concern that patients may not be getting a sufficient intramuscular dose of epinephrine. Mehr et al ⁵ demonstrated that

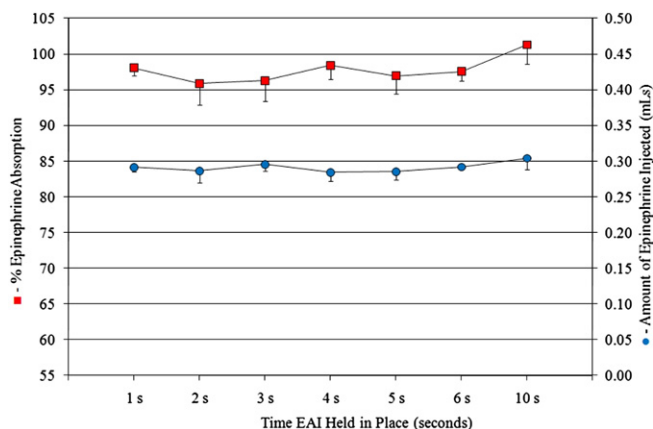


Figure 1. Relationship between the duration of injection and amount of epinephrine injected (circle) and the percentage of epinephrine absorbed by the marbled beef (square).

among junior and senior medical staff working at a tertiary pediatric hospital, only 2% of the physicians were able to accurately use an EAI training device.⁵ In this study, the most frequent error made by the house staff was not holding the pen in place for more than 5 seconds (57%). Sicherer et al⁴ assessed the correct use of self-administered EAI devices among food allergic adolescents, caregivers, and pediatricians and also reported a low success rate among participants using these devices. They found only 38% of patients or parents, 21% of attending pediatricians, and 36% of pediatric residents correctly demonstrated all steps in using an EAI device. Injecting and removing the pen device, rather than holding the device in place for several seconds, was a common mistake found in all groups. The authors noted that more than 50% of pediatricians and pediatric residents failed to hold the pen in place for the recommended period. In a recent study, Guerlain et al⁶ compared the usability and patient preference among 4 epinephrine autoinjectors: EpiPen, TwinJect, INT01 (prototype), and INT02 (prototype). Not holding the device in place for the correct amount of time (per manufacturers' instructions) was the most common error for each device. Specifically, of the 85 errors made by 48 participants using an EpiPen trainer, 40 (47%) errors were attributed to not holding the device in place for 10 seconds. Consequently, the new prototype devices (INT01, INT02) were designed to be held in place for 5 seconds.

To our knowledge, this is the first study to investigate the time required for an EAI to deliver epinephrine into muscle tissue. We investigated the actual time required for an EAI to deliver epinephrine into muscle tissue. We found no statistically superior amount of time to hold the EAI in place to achieve maximum epinephrine injection or absorption. Furthermore, there was no linear relationship between time and amount of epinephrine injected or absorbed into muscle tissue. These data suggest that holding the device in place for 1 second is as effective as 10 seconds.

The frequency of patients with anaphylaxis requiring multiple doses of epinephrine ranges from 13% to 35%, depending on the study.^{11–14} A prospective study by Scranton and colleagues¹¹ found 17 of 60 systemic reactions (28%) in patients receiving immunotherapy required a second dose of epinephrine to treat anaphylaxis symptoms soon after the first dose of epinephrine was given. In a retrospective medical review of patients presenting with anaphylaxis to health care professionals, Manivannan et al¹² reported that 27 of 208 patients (13%) required 2 or more doses of epinephrine for alleviation of symptoms. Korenblat et al¹³ found that among 105 anaphylactic episodes in 88 patients, 35.5% of patients with systemic reactions to inhalant allergen or Hymenoptera venom immunotherapy and live Hymenoptera stings required a second dose of epinephrine. Järvinen and colleagues¹⁴ reported that in 95 cases of systemic reactions among food allergic pediatric patients, 15 (16%) required 2 or 3 doses of epinephrine for cessation of symptoms.

Patients with asthma or with severe or protracted anaphylaxis are among those who often require multiple doses of epinephrine for alleviation of symptoms.³ Patient-specific risk factors identified with the increased likelihood of a severe or fatal anaphylactic event include patient age (infants, teens, and elderly), comorbid diseases (asthma, cardiovascular disease, allergic rhinitis, and mastocytosis), and concurrent medications (β -blockers and angiotensin-converting enzyme inhibitors).^{14–16} In addition, injecting an EAI using an incorrect technique is one of several reasons suggested to contribute to the lack of response to treatment with this drug.¹⁵ Other studies have demonstrated that the needle length may be insufficient to reach muscle in both adults and children, resulting in suboptimal administration of an epinephrine dose.^{17,18} Although our study did not specifically address the concern of needle length, the present study suggests that when patients require a second dose of epinephrine, it is not likely due to delivery of an insufficient dose of epinephrine injected, secondary to premature removal of the device, as previously hypothesized.^{5,15}

Among the limitations in this study is the use of marbled beef from a nonliving animal to simulate living human muscle tissue. Unlike dead tissue, living muscle tissue is vascular and aids in the distribution of epinephrine. In addition, tissue pressures in live muscle tissue may theoretically slow the injection of the drug from an EAI. Anterior compartment pressures measured immediately after maximal exercise effort have been reported to be 19.1 mm Hg and 12.2 mm Hg in runners and cyclists, respectively.¹⁹ The marbled beef pressures measured in this study were found to approximate values similar to living human muscle tissue. Therefore, we believe the results would be similar if studied in human participants. This study did not investigate other EAIs delivery into muscle tissue (ie, TwinJect). We believe other devices use similar delivery mechanisms of epinephrine, but our results should not be overgeneralized. Each EpiPen contains 2 mL of epinephrine solution. After an injection, approximately 1.7 mL of solution remains in the device and is

unusable. This likely accounts for results in excess of 0.3 mL or more than 100%, which we found at the 10-second time point.

Clinical effect of epinephrine was not investigated in this study. The optimal plasma and tissue concentration of epinephrine for successful treatment of anaphylaxis is not known.¹⁰ Clinical trials to investigate the optimal dose of epinephrine would be extremely difficult to perform given the unpredictable nature of anaphylaxis. Clinical response to epinephrine remains the ultimate outcome and determining factor for subsequent EAI injections.

In conclusion, continued education of proper EAI administration by health care professionals with the use of an EAI trainer as a visual tool is highly encouraged. Such education includes counseling the patient on the manufacturers' instructions regarding the duration an EAI device should be held in place. Our study's results suggest that patient's who pull out the device prematurely may still receive most of the epinephrine in the device after a single second and, as a result, may relieve some of the concern surrounding unintentional incorrect technique.

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