



Multicenter real-world experience with epinephrine 0.5 mg dosing for anaphylaxis with allergen immunotherapy

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Aim: To determine the safety and efficacy of 0.5 mg intramuscular (IM) epinephrine for the treatment of subcutaneous allergen immunotherapy induced anaphylaxis. **Patients & methods:** Retrospective chart review of patients who received 0.5 mg of IM epinephrine for treatment of anaphylaxis from subcutaneous allergen immunotherapy at two outpatient allergy and immunology practices. **Results:** Thirty-eight patients received 0.5 mg IM epinephrine. Eleven patients (29%) required a second dose, and two patients (5%) required a third dose of IM epinephrine. Sixteen patients (42%) were transferred to the emergency department with ongoing symptoms. All had eventual resolution of anaphylaxis. There were no adverse reactions or fatalities. **Conclusion:** IM epinephrine at a dose of 0.5 mg is safe and effective for treatment of anaphylaxis from subcutaneous allergen immunotherapy.

Lay abstract: The aim of this study to understand whether a 0.5 mg dose of epinephrine injected into the muscle is safe and effective in treating anaphylaxis (a life-threatening allergic reaction) caused by subcutaneous allergen immunotherapy (allergy shots). We reviewed the charts of all patients who received 0.5 mg of epinephrine at two allergy clinics. Thirty-eight patients received 0.5 mg of epinephrine. Twenty-nine percent of patients required a second dose of epinephrine and 5% required a third dose. Forty-two percent of patients were sent to the emergency department due to ongoing symptoms. Anaphylaxis was successfully treated in all patients. There were no side effects or deaths. Epinephrine at 0.5 mg is safe and effective in treating anaphylaxis from subcutaneous allergen immunotherapy.

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Keywords: allergies • anaphylaxis • dosing • efficacy • epinephrine • immunotherapy • intramuscular • safety • systemic reaction

Epinephrine is the first-line treatment for anaphylaxis, including systemic reactions (SRs), from subcutaneous allergen immunotherapy (SCIT) [1,2]. Anaphylaxis from SCIT occurs at a rate of 0.1% [3,4]. One in 9 million SCIT injections result in fatal anaphylaxis that is associated with delayed epinephrine administration [5,6]. However, the optimal dose of epinephrine in anaphylaxis is not well studied. The recommended dose is 0.01 mg/kg (maximum 0.5 mg) of a 1:1000 or 1 mg/ml solution administered intramuscularly (IM) [1]. However, epinephrine dosing recommendations by professional societies vary. In the USA, the maximum single dose recommended for adults is 0.3–0.5 mg and 0.3 mg for children [1,7]. However, in the UK and Australia, 0.5 mg is recommended for all adults and children over 12 years of age [8–10]. These dosing recommendations are based on little evidence, as studies of dose–response relationships and pharmacokinetic and pharmacodynamic data of epinephrine use in anaphylaxis are lacking [11,12].

At present, epinephrine autoinjectors are available in limited dosing options, making it difficult to deliver the recommended 0.01 mg/kg. In Canada, epinephrine autoinjectors are available in 0.15- and 0.3 mg doses, and

in October 2020, a 0.5 mg autoinjector became available. The 0.15 mg autoinjector is recommended for individuals weighing 7.5–30 kg whereas the 0.3 mg autoinjector is recommended for individuals weighing over 30 kg [13,14]. Common practice would be to transition to the higher dose when the individual is ~25 kg [15]. As per product monograph, the recommended dose of epinephrine for adults weighing more than 60 kg is 0.3–0.5 mg [14]. However, there are no data to inform who should receive the 0.3 mg versus 0.5 mg dose.

Additionally, there are limited studies evaluating outcomes among patients with immunotherapy-induced anaphylaxis or SCIT SRs after administration of IM epinephrine. In particular, the safety and efficacy of 0.5 mg epinephrine has never been assessed in SCIT SRs. Therefore, our objective was to review patient outcomes after administration of 0.5 mg IM epinephrine for treatment of SCIT SRs.

Materials & methods

We conducted a retrospective chart review of the electronic medical records of two Canadian outpatient allergy and immunology practices (one community and one hospital) for patients who received 0.5 mg IM epinephrine as the initial dose for treatment of a SCIT SR. Clinic notes were accessed to collect the following data: baseline patient characteristics (age, sex, comorbidities and medication use), treatment of SCIT SR (doses of IM epinephrine and adjunctive treatments) and patient outcomes (blood pressure, heart rate, time to symptom resolution and disposition). IM epinephrine was administered via needle and syringe from a vial of 1:1000 epinephrine. Counts and percentages were computed to summarize the data. Means and standard deviations (SD) were calculated for vital signs and time to symptom resolution. Data was analyzed using Microsoft Excel 2008. This study was a quality improvement initiative and therefore according to local policy (Tri-Council Policy Statement Article 2.5) did not require approval by the research ethics board.

Results

Baseline characteristics

We identified 38 patients between March 2006 and February 2020 who received 0.5 mg IM epinephrine as the initial dose for treatment of a SCIT SR. Results are presented in [Table 1](#). Twenty-eight patients were from a community allergy and immunology practice and ten patients were from a hospital allergy and immunology practice. The median age of patients was 34 years (interquartile range: 25–42 years). Most patients (84%) were over 18 years old. Males comprised 66% of the study population. Eleven patients (29%) had asthma. One patient was on an angiotensin-converting enzyme inhibitor (taken on the day of reaction).

Epinephrine doses & adjunctive treatments

Eleven patients (29%) required a second dose of IM epinephrine – nine (24%) received 0.3 mg and two (5%) received 0.5 mg as the second dose. Two patients (5%) required a third dose of IM epinephrine; both received 0.3 mg as their second and third dose. Cumulative doses of epinephrine received were as follows: 0.5 (71%), 0.8 (18%), 1 (5%) and 1.1 mg (5%). No patients were started on intravenous epinephrine in clinic. Other treatment modalities included bronchodilators (42%), intravenous fluids (37%), antihistamines (34%) and systemic steroids (11%).

Blood pressure & heart rate

Mean systolic blood pressure after administration of epinephrine was 120 mm Hg (SD $\pm$ 24). The highest documented systolic blood pressure was 155 mm Hg. Mean (SD) systolic blood pressure was 126 ($\pm$ 19), 95 ($\pm$ 30) and 122 ($\pm$ 15) mm Hg for patients who received cumulative epinephrine doses of 0.5, 0.8 and 1 mg or more, respectively.

Data on heart rate after administration of epinephrine was available for 35 patients. The mean heart rate was 98 beats per minute (SD $\pm$ 28). Mean (SD) heart rate was 95 ($\pm$ 22), 109 ($\pm$ 48) and 96 ($\pm$ 11) beats per minute for patients who received cumulative epinephrine doses of 0.5, 0.8 and 1 mg or more, respectively. The highest heart rate documented was 210 beats per minute. This patient received 0.5 mg of epinephrine followed by 0.3 mg. Given refractory hypotension despite the two doses (systolic blood pressure of 72 mm Hg), the patient was transferred to the emergency department (ED) for further observation. This patient was a healthy 32-year-old man, and there were no obvious risk factors for refractory anaphylaxis. He was subsequently discharged from the ED on the same day.

Table 1. Characteristics of patients and outcomes.

Patient characteristics	n = 38
Setting, n (%)	
Community allergy practice	28 (74)
Hospital allergy practice	10 (26)
Age (years)	
Median (IQR)	34 (25–42)
≥18, n (%)	32 (84)
Sex, n (%)	
Female	13 (34)
Male	25 (66)
Comorbidities, n (%)	
Asthma	11 (29)
Food allergy	7 (18)
Atopic dermatitis	7 (18)
History of SCIT SR	7 (18)
Medication use, n (%)	
ACE inhibitor	1 (3)
Beta-blocker	0 (0)
Oral antihistamine	6 (16)
Treatment of SCIT SR	
Second dose of IM epinephrine, n (%)	11 (29)
0.3 mg	9 (24)
0.5 mg	2 (5)
Third dose of IM epinephrine (0.3 mg), n (%)	2 (5)
Cumulative IM epinephrine dose, n (%)	
0.5 mg	27 (71)
0.8 mg	7 (18)
1 mg	2 (5)
1.1 mg	2 (5)
Adjunctive treatment, n (%)	
Bronchodilators	16 (42)
Intravenous fluids	14 (37)
Antihistamines	13 (34)
Systemic steroids	4 (11)
Patient outcomes	n = 38
Systolic blood pressure (mm Hg) after IM epinephrine, mean (SD)	
All patients (n = 38)	120 (±24)
Patients receiving 0.5 mg (n = 27)	126 (±19)
Patients receiving 0.8 mg (n = 7)	95 (±30)
Patients receiving ≥1.0 mg (n = 4)	122 (±15)
Heart rate (beats/minute) after IM epinephrine, mean (SD)	
All patients (n = 35)	98 (±28)
Patients receiving 0.5 mg (n = 25)	95 (±22)
Patients receiving 0.8 mg (n = 7)	109 (±48)
Patients receiving ≥1.0 mg (n = 3)	96 (±11)
Patient disposition, n (%)	
Symptom resolution in clinic and discharged home	11 (29)
Symptom resolution in clinic and sent to ED	11 (29)
Sent to ED with ongoing symptoms	16 (42)
ACE: Angiotensin-converting enzyme inhibitor; ED: Emergency department; IM: Intramuscular; IQR: Interquartile range; SCIT: Subcutaneous allergen immunotherapy; SD: Standard deviation; SR: Systemic reaction.	

Table 1. Characteristics of patients and outcomes (cont.).	
Patient characteristics	n = 38
Time to symptom resolution from first dose of IM epinephrine (min), n = 21	
Mean time (SD)	21 (±16)
≤5, n (%)	4 (19)
6–30, n (%)	13 (62)
31–60, n (%)	4 (19)
Continued SCIT, n (%)	30 (79)
ACE: Angiotensin-converting enzyme inhibitor; ED: Emergency department; IM: Intramuscular; IQR: Interquartile range; SCIT: Subcutaneous allergen immunotherapy; SD: Standard deviation; SR: Systemic reaction.	

Patient outcomes

Twenty-seven patients (71%) were transferred to the ED. All patients sent to the ED were from the community allergy practice except for one. Sixteen patients (42%) were sent to the ED with ongoing symptoms, and 11 patients (29%) had symptom resolution in clinic before transfer to the ED. Eleven patients (29%) were discharged home from the clinic with symptom resolution. There were no fatalities. Most patients (79%) continued to receive SCIT. Data on time to symptom resolution after administration of the first dose of epinephrine was available for 21 patients. The mean time to symptom resolution was 21 minutes (SD ± 16). The majority (81%) had symptom resolution within 30 minutes.

Discussion

Our study demonstrates that use of a 0.5 mg dose of IM epinephrine for SCIT SRs is safe and effective. There were no adverse reactions or fatalities. Most patients had resolution of symptoms in clinic and continued to receive SCIT. Our findings provide a real-world extension to the existing data on the pharmacokinetics and physiological impacts of 0.5 mg IM epinephrine. Two pharmacokinetic studies, one conducted among 18 healthy men [16] and the other among 12 teenagers at risk of food-induced anaphylaxis [17], found higher peak concentrations and bioavailability of IM epinephrine with use of the 0.5 mg dose compared with the 0.3 mg dose. In the former study, all participants reported experiencing expected pharmacological effects of epinephrine that included palpitations, tremors, paresthesias and headaches with no difference between the 0.3- and 0.5 mg groups [16]. The latter study reported no adverse events for either epinephrine dose [17]. The only study of the effects of 0.5 mg IM epinephrine during anaphylaxis was conducted among 22 adults with peanut-induced anaphylaxis. The authors found symptom resolution and improvement in respiratory function but limited effect on cardiovascular parameters, particularly stroke volume. Despite a small sample size limited to food-allergic patients who required only one dose of 0.5 mg epinephrine, the authors recommended the use of intravenous fluids in patients with refractory anaphylaxis because it resulted in a greater increase in stroke volume than 0.5 mg IM epinephrine [18]. Studies on response to epinephrine after immunotherapy induced anaphylaxis or SCIT SRs are limited. One study found resolution of symptoms among 28 patients with SCIT SR after use of IM epinephrine at cumulative doses ranging from 0.1 to 1 mg [19]. In our study, despite use of the recommended maximum initial dose of IM epinephrine at 0.5 mg, 29% of patients required a second or third dose of IM epinephrine. A recent systematic review showed that 8% of anaphylaxis events require multiple doses of epinephrine. This study excluded immunotherapy-induced anaphylaxis, however, and did not include data on dose and route of epinephrine [20]. Additionally, 42% of patients in our study were sent to the ED with ongoing symptoms. All but one patient sent to the ED were from the community allergy practice. Further studies are needed to investigate reasons for this discrepancy in ED transfer rates between community and hospital settings. Possible reasons include proximity to the nearest ED, lack of on-site emergency response teams and limited resources for monitoring and management of systemic reactions in the community setting compared with a hospital setting. Overall, there is a need for further studies to investigate appropriate initial and subsequent epinephrine dosing in SCIT SRs to decrease need for multiple epinephrine doses and rate of transfer to the ED. Particularly, studies comparing 0.5 mg with 0.3 mg are warranted, especially in the context of increasing availability of autoinjector dosing options.

Although patients in our study were administered IM epinephrine by healthcare professionals via needle and syringe, there may be a role for epinephrine autoinjector use in SCIT SR by patients. Approximately 20% of SRs in our study occurred 30 min after SCIT administration. One survey showed that only 29% of practices prescribed epinephrine autoinjectors to patients receiving SCIT, and these practices did not experience lower rates of delayed grade 3 or 4 SCIT SRs [5]. This was attributed to low rates of epinephrine autoinjector self-administration because only 8–26% of patients used their epinephrine autoinjector for a delayed SCIT SR. However, data on autoinjector dose prescribed were not available. Additionally, a separate study revealed that universal prescription of epinephrine autoinjectors in patients receiving SCIT was not cost-effective [21], but may be beneficial in patients at high risk of SCIT SR [22].

Our study has a few limitations. Due to small sample size, our study was not powered to detect differences in blood pressure and heart rate based on cumulative epinephrine doses. Data collection was retrospective and, as such, we were unable to acquire pharmacokinetic data. Additionally, data on site of IM epinephrine injection, needle length and confirmation of IM deposition using ultrasound were unavailable. Finally, for the 27 patients sent to the ED, information on further management in the ED was unavailable.

Conclusion

IM epinephrine dosed at 0.5 mg is safe and effective for the treatment of immunotherapy-induced anaphylaxis. However, further studies on optimal initial dosing of IM epinephrine are necessary to reduce the need for repeat epinephrine doses and ED visits due to refractory anaphylaxis.

Summary points

- The optimal dose of intramuscular (IM) epinephrine for the treatment of anaphylaxis including allergen immunotherapy-induced anaphylaxis is unknown.
- The recommended initial dose for adults is 0.3–0.5 mg.
- We assessed safety and efficacy of 0.5 mg IM epinephrine in the treatment of allergen immunotherapy-induced anaphylaxis in 38 individuals.
- Use of 0.5 mg IM epinephrine for treatment of allergen immunotherapy-induced anaphylaxis was safe; there were no adverse events and no fatalities.
- IM epinephrine at a dose of 0.5 mg was generally effective in treating allergen immunotherapy-induced anaphylaxis.
- Twenty-nine percent of patients required more than one dose of intramuscular epinephrine.
- Forty-two percent of patients required transfer to the emergency department for ongoing symptoms.
- There is a need for further studies to assess the optimal initial dose of IM epinephrine for treatment of allergen immunotherapy-induced anaphylaxis.

Author contributions

S Jeimy, F White, W Moote, M Kuprowski and H Kim contributed to data acquisition. A Quidwai and N Rondilla performed chart reviews. N Correa and H Kim performed data analysis. N Correa, S Jeimy and H Kim contributed to study design and drafted the manuscript. All authors provided critical review of the manuscript for important intellectual content. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work related to its accuracy or integrity.

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S Jeimy has been on speaker's bureaus for Aralez, Novartis, Astra Zeneca and Sanofi and on the advisory board for Sanofi. H Kim has been on speaker's bureaus and/or advisory boards for ALK, Aralez, Astra Zeneca, GSK, Kaleo, Mylan, PEDIAPHARM, Pfizer and Stallergenes Greer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This study was a quality improvement initiative and therefore according to local policy (Tri-Council Policy Statement Article 2.5) did not require approval by the research ethics board.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

- Shaker MS, Wallace DV, Golden DBK *et al.* Anaphylaxis – a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. *J. Allergy Clin. Immunol.* 145(4), 1082–1123 (2020).
- Cox L, Nelson H, Lockey R *et al.* Allergen immunotherapy: a practice parameter third update. *J. Allergy Clin. Immunol.* 127(Suppl. 1), S1–S55 (2011).
- Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008–2012: an update on fatal and nonfatal systemic allergic reactions. *J. Allergy Clin. Immunol. Pract.* 2(2), 161–167.e3 (2014).
- Robertson K, Montazeri N, Shelke U *et al.* A single centre retrospective study of systemic reactions to subcutaneous immunotherapy. *Allergy Asthma Clin. Immunol.* 16(1), 1–6 (2020).
- **Systemic reactions to subcutaneous allergen immunotherapy requiring epinephrine occur at a rate of 0.1% of injection visits.**
- Epstein TG, Liss GM, Berendts KM, Bernstein DI. AAAAI/ACAAI subcutaneous immunotherapy surveillance study (2013–2017): fatalities, infections, delayed reactions, and use of epinephrine autoinjectors. *J. Allergy Clin. Immunol. Pract.* 7(6), 1996–2003.e1 (2019).
- Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990–2001. *J. Allergy Clin. Immunol.* 113(6), 1129–1136 (2004).
- Lieberman P, Nicklas RA, Randolph C *et al.* Anaphylaxis – a practice parameter update 2015. *Ann. Allergy Asthma Immunol.* 115(5), 341–384 (2015).
- Ewan P, Brathwaite N, Leech S *et al.* BSACI guideline: prescribing an adrenaline auto-injector. *Clin. Exp. Allergy* 46(10), 1258–1280 (2016).
- Resuscitation Council UK. Emergency treatment of anaphylactic reactions: guidelines for healthcare providers (2016). www.resus.org.uk/library/additional-guidance/guidance-anaphylaxis/emergency-treatment
- Australasian Society of Clinical Immunology and Allergy (ASCIA). Acute management of anaphylaxis (2021). www.allergy.org.au/images/ASCIA_HP_Guidelines_Acute_Management_Anaphylaxis_2021.pdf
- Dreborg S, Kim H. The pharmacokinetics of epinephrine/adrenaline autoinjectors. *Allergy Asthma Clin. Immunol.* 17(1), 1–11 (2021).
- Moss J, Jani Y, Edwards B *et al.* Pharmacokinetic and pharmacodynamic evidence of adrenaline administered via auto-injector for anaphylactic reactions: a review of literature. *Br. J. Clin. Pharmacol.* 87(3), 816–824 (2021).
- Mylan Specialty L.P. Prescribing information EpiPen (2017). https://pdf.hres.ca/dpd_pm/00039519.PDF
- Bausch Health Canada Inc. Prescribing information Emerade (2020). https://pdf.hres.ca/dpd_pm/00051244.PDF
- Sicherer SH, Simons FER, Mahr TA *et al.* Epinephrine for first-aid management of anaphylaxis. *Pediatrics* 139(3), e20164006 (2017).
- Duvauchelle T, Robert P, Donazzolo Y *et al.* Bioavailability and cardiovascular effects of adrenaline administered by anapen autoinjector in healthy volunteers. *J. Allergy Clin. Immunol. Pract.* 6(4), 1257–1263 (2018).
- **Use of 0.5 mg intramuscular epinephrine resulted in higher peak concentrations and bioavailability of epinephrine compared with 0.3 mg in 18 healthy men.**
- Patel N, Isaacs E, Duca B *et al.* What dose of epinephrine? Safety and pharmacokinetics of 0.5 mg versus 0.3 mg epinephrine by autoinjector in food-allergic teenagers: a randomized cross-over trial. *J. Allergy Clin. Immunol.* 145(2), AB6 (2020).
- **Use of 0.5 mg intramuscular epinephrine resulted in higher peak concentrations and bioavailability of epinephrine compared with 0.3 mg in 12 teenagers at risk of food-induced anaphylaxis.**
- Turner PJ, Ruiz-Garcia M, Durham SR, Boyle RJ. Limited effect of intramuscular epinephrine on cardiovascular parameters during peanut-induced anaphylaxis: an observational cohort study. *J. Allergy Clin. Immunol. Pract.* 9(1), 527–530.e1 (2021).
- **Use of 0.5 mg intramuscular epinephrine resulted in symptom resolution and improvement in respiratory function but had limited effect on cardiovascular parameters, particularly stroke volume among 22 adults with peanut induced anaphylaxis.**
- Phillips JF, Lockey RF, Fox RW *et al.* Systemic reactions to subcutaneous allergen immunotherapy and the response to epinephrine. *Allergy Asthma Proc.* 32(4), 288–294 (2011).
- **Use of intramuscular epinephrine at cumulative doses ranging from 0.1 to 1 mg resulted in resolution of symptoms among 28 patients with systemic reactions to subcutaneous allergen immunotherapy.**
- Patel N, Chong KW, Yip AYG *et al.* Use of multiple epinephrine doses in anaphylaxis: A systematic review and meta-analysis. *J. Allergy Clin. Immunol.* 21, doi:10.1016/j.jaci.2021.03.042 (2021) (Epub ahead of print).

21. Sun D, Cafone J, Shaker M, Greenhawt M. The cost-effectiveness of requiring universal vs contextual self-injectable epinephrine autoinjector for allergen immunotherapy. *Ann. Allergy Asthma Immunol.* 123(6), 582–589 (2019).
22. Bernstein DI, Epstein TEG. Safety of allergen immunotherapy in north America from 2008–2017: lessons learned from the ACAAI/AAAAI National Surveillance Study of adverse reactions to allergen immunotherapy. *Allergy Asthma Proc.* 41(2), 108–111 (2020).