



Letter

Experience with epinephrine delivery in immunotherapy-associated systemic reactions

The administration of subcutaneous immunotherapy (SCIT) is associated with a 0.06% to 0.67% risk of systemic reactions (SRs).^{1,2} Injectable epinephrine is first-line treatment for SRs specified in anaphylaxis and allergy immunotherapy practice parameters.³ Historically, the deltoid muscle has been used to deliver epinephrine for asthma and anaphylaxis. Two pharmacokinetic studies performed in 17 children and 13 adults reported faster peak plasma epinephrine levels with intramuscular epinephrine delivered to the vastus lateralis compared with the deltoid muscle.^{4,5} Nevertheless, the deltoid remains an injection site used in many institutions, and no clinical evidence suggests epinephrine is ineffective in the deltoid. These observations highlight the need for clinically relevant studies on epinephrine delivery practices in SCIT-associated SRs.

This 7-year study (2005–2012) approved by an institutional review board examined epinephrine administration at a single institutional allergy clinic. All SCIT-associated SRs identified and treated with at least 1 dose of epinephrine were included. SRs that were not treated with epinephrine and reactions attributable to non-SCIT triggers were excluded. In our clinic, 2 epinephrine modalities were used: epinephrine prefilled syringes (EPFSs) and auto-injectors. EPFSs were drawn up daily in 3 doses (0.15, 0.3, and 0.5 mg). EPFSs were injected intramuscularly using 2.5-cm-long 25-gauge hypodermic safety needles injected in the deltoid or vastus lateralis. Adult and pediatric epinephrine auto-injectors (EpiPen, Mylan, Canonsburg, Pennsylvania) were administered according to the package insert.

During the study, 1,328 patients undergoing SCIT received 93,136 injections of aeroallergen and venom immunotherapy (SR rate of 0.28% per injection, 16.9% per patient). Most received the first intramuscular epinephrine dose from an EPFS (99%) injected in the deltoid (96%; Table 1). The average time to first epinephrine administration was 8.2 minutes from symptom onset. The mean time to resolution of symptoms after the last epinephrine was 24.2 minutes. No difference in time to resolution of symptoms was observed for epinephrine injected in the deltoid vs the vastus lateralis (24.1 vs 24.4 minutes, $P = .9728$). The mean post-epinephrine observation time was 70.5 minutes. Most reactions (95%) were treated with full resolution of symptoms and observed for shorter than 2 hours. SRs with ongoing symptoms were transferred to the emergency department (2.6%). No deaths occurred.

The SRs treated with more than 1 dose of epinephrine demonstrated a longer time to resolution of symptoms and higher grade

severity (odds ratio 2.4, $P < .0001$; Table 1). When the reaction was grade 1 or 2, 97% (247 of 255) of the first epinephrine doses were given in the deltoid; for grade 3 or 4 reactions, 73% (8 of 11) were administered in the deltoid ($P = .0001$). For the second epinephrine doses, 79% (56 of 71) were injected in the deltoid and 20% (14 of 71) were injected in the vastus lateralis in patients with grade 1 or 2 SRs. In those with grade 3 or 4 SRs, 50% (5 of 10) of injections were administered in the vastus lateralis ($P = .012$). For the third epinephrine dose, the deltoid was used in 86% (6 of 7) of grade 1 or 2 SRs, whereas vastus lateralis administration increased for grade 3 or 4 reactions (3 of 5, 60%, $P = .011$).

To our knowledge, this is the first study focused on epinephrine delivery modality and anatomic injection site in patients experiencing SCIT-associated SRs. These data show that the administration of the first epinephrine dose by EPFS intramuscularly in the deltoid is a clinically effective initial treatment for SCIT-associated SRs. In this population, most patients with SRs were discharged home within 2 hours after treatment, reflecting a favorable resolution of most SRs.

Secondary measures of clinical effectiveness include time to first epinephrine delivery (8.2 minutes), which was faster than the 24-minute average epinephrine delivery time reported in a hospital setting.⁶ The rate of second epinephrine administration in our cohort (30.5%) is similar to those previously reported (16%–36%).^{1,2,7} Patients with more severe and prolonged symptoms received more epinephrine, consistent with previously reported findings.⁶ Time to symptom resolution was comparable between deltoid and vastus lateralis administration, indicating similarity in clinical response.

There remains limited clinical data comparing different epinephrine modalities. Current practices vary and include drawing up epinephrine at the time it is needed, auto-injectors, and EPFSs. In the allergy clinic, there is no evidence that one delivery modality is preferable to another. The EPFS offers unique advantages over the auto-injector, with increased flexibility associated with injection site, dosing options, and needle length. The EPFS can be administered in the deltoid or vastus lateralis; in our population, the EPFS allowed clinicians to deliver an immediate initial epinephrine dose in the deltoid and the flexibility to transition to the vastus lateralis and/or administer the 0.5-mg epinephrine dose if needed. The standard needle length used in our EPFS is 1 cm longer than in the EpiPen. This needle length advantage addresses concern about obesity and auto-injector needle length inadequacy, because in one study the auto-injector needle was not long enough to reach the vastus lateralis in 30% of children weighing at least 30 kg,⁸ and an adult study found similar rates (31%) of needle length inadequacy.⁹ In contrast, the EPFS allows the flexibility of attaching needles of adequate length.

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Table 1
Epinephrine delivery in SCIT-associated SRs

Total SCIT-associated SRs, N	266
Doses of epinephrine administered, n (%)	
1	266 (100)
2	81 (30.5)
3	12 (4.5)
Reactions administered 1 dose of epinephrine (n = 266)	
WAO grade severity, n (%)	
1 or 2	255 (96)
3 or 4	11 (4)
Location of epinephrine delivery, n (%)	
Deltoid	254 (96)
Vastus lateralis	6 (2)
Unknown	6 (2)
Modality of epinephrine, n (%)	
EPFS	263 (99)
Auto-injector	3 (1)
Time to first dose of epinephrine (min)	
Mean $\pm$ SD	8.2 $\pm$ 15.4
Median	3
Time to symptom resolution (min)	
Mean $\pm$ SD	19.6 $\pm$ 15.8
Median	14
Reactions administered 2 doses of epinephrine (n = 81)	
WAO grade severity, n (%)	
1 or 2	71 (88)
3 or 4	10 (12)
Location of epinephrine delivery, n (%)	
Deltoid	60 (74)
Vastus lateralis	19 (23)
Unknown	2 (3)
Modality of epinephrine, n (%)	
EPFS	79 (98)
Auto-injector	2 (2)
Time to second dose of epinephrine (min) ^a	
Mean $\pm$ SD	5.5 $\pm$ 8.9
Median	2
Time to symptom resolution (min)	
Mean $\pm$ SD	35 $\pm$ 24.7
Median	28
Reactions administered 3 doses of epinephrine (n = 12)	
WAO grade severity, n (%)	
1 or 2	7 (58)
3 or 4	5 (42)
Location of epinephrine delivery, n (%)	
Deltoid	6 (50)
Vastus lateralis	4 (33)
Unknown	2 (17)
Modality of epinephrine, n (%)	
EPFS	7 (58)
Auto-injector	5 (42)
Time to third dose of epinephrine (min) ^a	
Mean $\pm$ SD	34.6 $\pm$ 13.5
Median	36
Time to symptom resolution (min)	
Mean $\pm$ SD	66 $\pm$ 22.6
Median	66

Abbreviations: EPFS, epinephrine prefilled syringe; SCIT, subcutaneous immunotherapy; SRs, systemic reactions; WAO, World Allergy Organization.

^aTime to dose 2 or 3 is based on time since previous dose (1 or 2, respectively).

As the demand for epinephrine auto-injectors has increased, the cost of epinephrine auto-injectors also has increased markedly over time.¹⁰ In our institution, the cost of an EpiPen or

EpiPenJr (2-pak) is \$175.99 (\$88/dose; \$37,136 during the entire 7-year study). In contrast, the daily supply cost of EPFSs (3 syringes at 0.15, 0.3, and 0.5 mg) is \$2.04 (\$3,945 during the entire study).

Although we report the advantages of the EPFS for SCIT-associated SRs in the allergy clinic, we do not speculate on the utility and the lifesaving importance of epinephrine auto-injectors in diverse settings. Study limitations include the retrospective design, and the small number of severe grade 3 or 4 reactions could limit its applicability. At the same time, most mild grade 1 or 2 reactions suggest an efficient first epinephrine delivery that stops symptom progression, supporting the effectiveness of our approach.

In the allergy clinic, the deltoid remains a viable site for the first epinephrine delivery. EPFSs are a practical and effective option, demonstrating advantages in cost savings and increased flexibility with injection site, dosing options, and needle length in the initial treatment of SCIT-associated SRs.

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