

Epinephrine Needle Length in Autoinjectors and Why It Matters



T. Ted Song, DO *Seattle, Wash*

Fatalities from anaphylaxis are rare but real. To prevent fatalities, the prompt administration of epinephrine (not antihistamines or corticosteroids) is the treatment of choice.¹ All international guidelines recommend the intramuscular (IM) route in the lateral thigh as the preferred route and site of administration. Simons et al² showed in healthy adult individuals that IM injection reached quicker time to peak plasma concentration (T_{max}) and higher peak plasma concentration (C_{max}) than subcutaneous (SQ) injection.² Similar results were observed in pediatric studies.³ Further study of IM and SQ epinephrine injections in the real-life setting of anaphylaxis would be helpful, but because of ethical concerns this study is not possible. Based on these studies, IM injection into the vastus lateralis muscle appears to be the preferred delivery of epinephrine.

Delivery depth of epinephrine is affected by many factors such as needle length, sex, force of propulsion, and obesity (skin to muscle depth). There are multiple different epinephrine autoinjectors on the market with varying preinjection needle lengths. Epinephrine 0.15 mg autoinjector needle lengths range from 1.17 to 1.6 cm. For epinephrine 0.30 mg, the needle lengths range from 1.17 to 2.5 cm. Studies show that the tip of the needle is not where the epinephrine is delivered. A pig model study demonstrated that epinephrine was delivered beyond the needle length.⁴ The delivery extended to almost twice the distance of the needle length. This was due to propulsive forces and compression of the tissue. To trigger an autoinjector, pressure must be applied. In the case of EpiPen, 2 to 8 lb of pressure is needed to trigger the device. This added pressure compresses the SQ tissue, decreasing the skin to muscle depth. In addition, the tightly coiled spring inside the autoinjector delivers a force of 22.7 lb for EpiPen and 23.6 lb for EpiPen Jr.⁵ These 2 factors in the EpiPen deliver epinephrine beyond the length of the needle.

Another factor that contributes to the adequate delivery of epinephrine is the sex differences in the SQ tissue depth. Computed tomography scans of the anterolateral thigh show that the SQ tissue depth is greater for females than for males. The

anterolateral thigh subcutaneous tissue depth (SCTD) for males is 0.66 ± 0.47 cm (range, 0.21-3.47 cm) and for females 1.48 ± 0.72 cm (range, 0.24-3.71 cm).⁶ Another study measured gluteal SQ fat thickness for gluteal muscle delivery of vaccines. The average gluteal fat thickness for females was 3.32 cm (range, 0.83 to 8.15 cm), whereas the average for the male was 2.31 cm (range, 0.11-8.04 cm).⁷ Based on these data, a longer needle maybe needed in females to deliver epinephrine to the IM space.

As obesity continues to rise, there is concern that the needle length may be too short in some patients. UK's Resuscitation Council recommends administering epinephrine with syringe and needle by a medical provider when possible. The council recommends the use of a needle length of 2.5 or 3.8 cm for IM delivery in adults.⁸ In select European countries, an epinephrine autoinjector with a needle length of 2.5 cm is available. Access to a longer needle may help patients with different body mass index and sex deliver epinephrine beyond the SQ space and into the muscle.

However, in pediatric studies, there are concerns that the needle length available in the autoinjector may be too long. A study examined 53 infants and toddlers weighing 7.5 to 15 kg. They applied 10 lb of compression to Auvi-Q with a needle length of 1.27 cm and noted that 43.1% of children would likely receive injection in the bone.⁹ This observation has highlighted a need for an autoinjector with a shorter needle length for children weighing less than 15 kg. These and other similar studies have identified the need for both longer and shorter needle lengths for patients with different weights and body mass indices.

In this issue of *The Journal of Allergy and Clinical Immunology: In Practice*, Duvauchelle et al¹⁰ show that there are factors other than needle length that may contribute to the bioavailability of epinephrine. Among nonobese males, Anapen with a needle length of 1.05 cm had similar T_{max} but C_{max} was higher than that produced by injection via a syringe with a needle length of 2.54 cm. This suggests that tissue compression and the propulsive force of the autoinjector may play a larger role than the length of the needle. Another study showed that the autoinjector's needle length may be crucial if the needle length is short and epinephrine may not penetrate the fascia surrounding the thigh.¹¹ This would result in SQ rather than IM delivery. It is likely that the propulsive force may be sufficient in some instances to propel epinephrine across the fascia into the IM space.¹² This may be a possible explanation for the bioavailability reported by Duvauchelle et al. Also, Duvauchelle et al found that 11 of 12 overweight women receiving SQ epinephrine demonstrated superior bioavailability than normal-weight men who received IM epinephrine. Females had a higher C_{max} and area under the curve (0-240 min) than did males. Surprisingly, they had a similar T_{max} . These unexpected findings suggest that there

Division of Allergy and Infectious Disease, University of Washington, School of Medicine, Seattle, Wash

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Corresponding author: T. Ted Song, DO, Division of Allergy and Infectious Diseases, University of Washington, School of Medicine, 750 Republican St, Box 358061, Seattle, WA 98109. E-mail: Tsong@allergyasthma.washu.edu.

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may be other factors such as hormonal influences affecting the pharmacokinetics of this drug. Still more studies need to be performed as to why $T_{\max}$ and $C_{\max}$ were not consistently elevated with 1 delivery device.

The package inserts for many epinephrine autoinjectors state that both the SQ and IM modes of delivery are acceptable. As clinicians, it is imperative that anaphylaxis be identified, and epinephrine administered promptly. Delay in the administration of epinephrine has been one of the key reasons for fatalities in anaphylaxis. It is important not only to deliver it in a timely manner but also to deliver it to the right tissue space. IM administration (via the vastus lateralis, but not the deltoid) results in quicker $T_{\max}$: 8 minutes for IM in the vastus lateralis muscle vs 34 minutes for SQ delivery.^{2,3} In addition, IM administration via the vastus lateralis muscle results in a higher $C_{\max}$ compared with the SQ or deltoid route. These data show that IM delivery increases $T_{\max}$ more than 4× faster than SQ delivery. When time to epinephrine administration is crucial to prevent fatalities, why would clinicians settle for the slower SQ delivery? Adequate needle length is necessary to deliver epinephrine to the IM space. Compression, propulsion, and skin to muscle depth as well as possibly sex all play a role in the bioavailability of epinephrine. Duvauchelle et al suggest that there may be more factors that have not been elucidated that may play a role. This emphasizes the need for more research in needle length and proper delivery of epinephrine. This indeed will make a difference between life and death.

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