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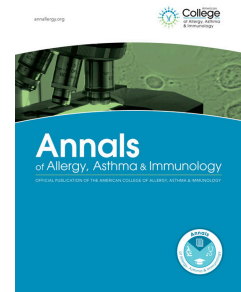
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Epinephrine autoinjectors - the needle length matters

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Short title: The needle length matters

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Epinephrine autoinjectors should be used for treatment of severe general allergic reactions in the community. Recently, there has been a concern that the autoinjectors are not designed properly for all patients.

Autoinjector needle length has been a topic of discussion since Simons et al. showed that intramuscular injection in the mid antero-lateral thigh causes a serum peak (C_{max}) of 5-10 minutes with, in some cases, an additional peak after 40-50 minutes. Subcutaneous injection was followed by a T_{max} at 15-20 minutes. Simons et al. noted this second peak after injection with Epipen® in adults. Injection by syringe, with needle of unconfirmed length, showed only one peak at 5-10 minutes. The second peak may indicate subcutaneous injection or it may occur due to an early vasoconstriction with secondary epinephrine release. Anaphylaxis develops rapidly, so the early peak after intramuscular injection is most important. Duvauchelle et al., injected 12 obese women with an epinephrine autoinjector with very short needle, Anapen®. Ten of 12 obese women were confirmed to have an ultrasound visible deposit of epinephrine in the subcutaneous tissue and a late group-averaged peak concentration, C_{max} . These data suggests that epinephrine autoinjectors should deliver epinephrine intramuscularly to achieve an early C_{max} .

In 2005, Song et al. using computed tomography in patients investigated for other reasons than anaphylaxis, found the subcutaneous tissue depth was too great to lead to intramuscular injections. Later, ultrasound has been used to investigate the skin to muscle (fascia)(STMD) and skin to bone(periosteum) (STBD) distances. To study the autoinjector needle length in relation to STBD and STMD, Kim started the most extensive ultrasound study in patients with anaphylaxis including 401 children, adolescents and adults with confirmed food allergies. To mimic high pressure epinephrine auto-injectors, approximately 8 lb or 35 Newtons was applied and minimal pressure was applied to the ultrasound probe to mimic low pressure epinephrine auto-injectors. The ultrasound probe did not exactly match the footprint of the auto-injectors. By using the mean needle lengths as reported in the product specifications, we first found that, using high pressure epinephrine auto-injectors, small children had a high risk of intraosseous/periosteal injection and that there was a risk of subcutaneous injection most pronounced in adult women. We also found that 90% of the tissue compression caused

by high pressure was of the muscle and only 10 % of the subcutaneous tissue. Thus, the STMD was not impacted as much by compression as skin to bone distance.

Manufacturers generously supplied us with data on the variation in needle length accepted for batch release for their specific products. The allowed variation differed between the epinephrine auto-injectors. This variation was 5 mm for Epipen/Epipen Jr[®], 2.6 mm for Auvi-Q[®] and for Emerade[®] 1.7 to 1.5 mm (1). The risk of intraosseous/periosteal injection was greatest in small children using needles with the maximal allowed needle length for Epipen/Epipen Jr[®]. The newly introduced Auvi-Q[®] 0.1 mg with a shorter needle had no risk of bone injection but a high risk for subcutaneous injection. Using skin to bone distance from our studies, we first defined the longest needle not causing intraosseous/periosteal injection, “ideal” skin to bone distance. We did not use the length of needles used in the present s, but applied the “ideal” skin to bone distance needle length to our data on skin to muscle distance. Then, we added data on the brand-specific variation in needle length obtained from manufacturers as well as three extra millimeters for thick clothing, to illustrate the risk of subcutaneous injection using the “ideal” STBD needles, Figure 1 (2). With the variation in length accepted by manufacturers at present there is no chance to find a needle length of high pressure epinephrine auto-injectors with both a low risk of intraosseous/periosteal injection and a low risk of subcutaneous injection. On the other hand, currently available low pressure epinephrine auto-injector needle lengths are likely to inject epinephrine intramuscular although there is still a risk of subcutaneous injections in some overweight and obese patients.

Another important issue regarding needle length is that injecting through thick winter clothes decreased the risk of intraosseous/periosteal injection and increased the risk for subcutaneous injection in all age groups (3). The Auvi-Q[®] 0.1 mg with a shorter needle caused subcutaneous injection in most young children.

We also asked the manufacturers for data on the variation in pressure that should be applied to their epinephrine auto-injectors and accepted for batch release (4). The high pressure we applied to mimic the pressure on high pressure epinephrine auto-injectors, 35 Newtons, was within the range of the

accepted variation for Epipen[®]/Epipen Jr[®] and Auvi-Q[®]. The low pressure applied to the ultrasound probe to mimic the pressure applied for release of the needle of the LPEAI Emerade[®] was the minimal pressure required to obtain an adequate ultrasound image.

We completed ultrasound determinations of the skin to bone distance and skin to muscle distance in 401 patients of all ages with food allergy to illustrate the ability of EAI injections to reach the muscle. We found the pressure on high pressure epinephrine auto-injectors compresses mainly the muscle, the longest needle accepted for batch release increases the risk for intraosseous/periosteal injection and decreases the risk of subcutaneous injection, high pressure epinephrine auto-injectors have an increased risk of intraosseous/periosteal injection, with the exception of Auvi-Q[®] 0.1 mg. This device had a high risk of subcutaneous injection. Furthermore, we found that injection through thick clothes increases the risk of subcutaneous injection and decreases the risk of intraosseous/periosteal injection. We have not yet studied the variation of pressure applied to the autoinjectors.

We suggest that patients at risk of anaphylaxis who are thin are prescribed an autoinjector with relatively short needle. Overweight patients and many women, should be prescribed a low pressure epinephrine autoinjector with longer needle length to increase the chance of an intramuscular injection.

We feel it is imperative to perform well designed studies on epinephrine pharmacokinetics. Furthermore, new ultrasound studies with brand-specific data on pressure variation(4), and needle length variation should be performed using probes with brand specific probe footprints. In children and adolescents there is a need for z-scores on age and weight and in adults, z-scores for weight of adult women.

In conclusion, we believe it is impossible to find one needle length for high pressure epinephrine auto-injectors that avoids intraosseous/periosteal injection and has a low risk of subcutaneous injection in all patients. Low pressure epinephrine auto-injectors that compress the muscle less can use longer needles and therefore reach the muscle in the vast majority. Finally, future studies should include the influence of the variation in pressure needed to release the needles of EAIs. Importantly, even though

80 currently available epinephrine auto-injectors may not deliver the drug intramuscularly in all patients,
81 they should be used since subcutaneous injection is better than not giving epinephrine at all.

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83 Further references are available in an online supplement

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Figure 1 To the left are plotted individual STBD of 401 patients versus weight (grey dots).

Approximate limits of STBD/maximum needle length that will not hit the bone.

To the right are plotted individual STMD of the same 401 patients versus weight (red dots). The solid green line is at the same depth as the red line on the left. The dashed line indicates the corresponding shortest needle of Epipen[®] accepted for batch release which is 5 mm shorter than the longest accepted needle. The dotted lines indicate the depth penetrated by the shortest acceptable needle length when injecting through thick winter clothing.

Figur 1.

