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Tissue compression and epinephrine deposition



To the Editor:

In his editorial “Epinephrine needle length in autoinjectors and why it matters” in the *Journal of Allergy and Clinical Immunology: In Practice*, Song¹ reviewed the findings of Duvauchelle et al,² reporting new data on the pharmacokinetics of epinephrine and epinephrine autoinjectors (EAI). We disagree with a number of Song’s interpretations of earlier studies.

First, Song claims that when using an EAI, epinephrine is not deposited at the tip of the needle but forced further by high pressure. This finding is from a pig model study where there was no assessment of the impact of muscle fascia. Importantly, Diacono et al³ found that the propulsive force of autoinjectors did not propel the epinephrine through the fascia using a pig model. We agree with the data by Diacono et al suggesting that the needle must pass through the whole muscle fascia and the epimysium to deliver epinephrine into muscle (IM).

Secondly, Song claims that the subcutaneous (SC) tissue is compressed by the injection pressure from autoinjectors. It is true that some compression of SC tissue occurs. But on average only 10% of the compression is in the SC tissue and approximately 90% of the compression takes place in the muscle⁴ (Table I). So compression has a relatively small impact on successful IM delivery. The SC tissue is more compressed in women than in men.

Thirdly, Song¹ claims that “It is likely that the propulsive force may be sufficient in some instances to propel epinephrine across the fascia into the IM space” without providing any evidence. We do not believe that EAI given SC will deliver the drug intramuscularly. Song cites Diacono et al,³ who identified that the epinephrine jet does not penetrate the fascia. However, Song

TABLE I. New data from the original papers analyzing STMD, STBD min and max and % compression of the subcutaneous tissue in adult women (n = 67) and men (n = 32)

Variable	n	Mean	Min	Max	Significances
STMD _{min} women	67	15.4	6.0	31.7	<.000001 Women STMD _{min} vs STMD _{max}
STMD _{min} men	32	6.9	3.3	13.6	
STMD _{max} women	67	12.9	5.0	27.7	<.000001 P ≤ .000001 Men STMD _{min} vs STMD _{max}
STMD _{max} men	32	6.3	2.7	13.7	
Compression SC % women	67	15.8	−9.5	48.8	<.000001 P ≤ .000001
Compression SC % men	32	3.2	−1.8	13.0	

SC, Subcutaneous; STMD, skin to muscle distance; STBD, skin to bone distance. *t*-tests were performed.

did not use Diacono et al’s findings when stating his claims. Furthermore, in Duvauchelle et al’s study,² imaging of SC injections does not appear to lead to ultrasound changes in the IM compartment. This suggests that the SC epinephrine did not penetrate into muscle.

Lastly, Song claims that estrogens may influence the pharmacokinetics of epinephrine when assessed in these studies that span several minutes only. We cannot rationalize how estrogen would impact epinephrine levels in such studies. We could not find any evidence in the medical literature to support this idea.

We conclude that until further human experiments have been performed, the pig model data showing that epinephrine is not forced through the fascia by the high jet pressure should be accepted, that the compression of the SC tissue by EAI is limited, and that there seems to be little difference in tissue compression between men and women.

Sten Dreborg drafted the correspondence and Harold Kim and Sten Dreborg reviewed the text critically and accepted the final version.

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Reply

To the Editor:

We appreciate comments from Dreborg and Kim.¹ We value their input, but there are additional data that challenge their conclusions. We discuss these data below.

Diacono et al² state that deep fascia acts as an impermeable barrier to fluid movement. Dreborg and Kim agree with Diacono et al that the propulsive force of autoinjectors does not propel the epinephrine through the fascia. We disagree with this statement. There are multiple needle-free devices that generate fine streams of high-pressure propelled fluid that deliver medications to different tissue spaces including to the muscle. Zetajet is one example of a needle-free device that received FDA approval for subcutaneous (SQ) and intramuscular (IM) delivery of vaccines and medications in 2009.³ The high-pressure fluid generated by the spring inside the device can penetrate the skin, fascia, and into muscle without using a needle. In fact, by adjusting the propulsive force, Zetajet can deliver to SQ, IM, and even to the intradermal space demonstrating the importance of propulsive force in determining delivery depth.^{4,5} Furthermore, there are a variety of different needle-free devices that generate propulsive force by the use of gas chambers, electromagnetic force, and shock waves.⁶ This clearly shows that fascia is penetrable even without the necessity of needle penetration below this surface, and that propulsive force is a crucial factor determining delivery depth even without the use of a needle.

One might ask why then is there no needle-less device for epinephrine delivery? Actually, such a device does exist. Zeneo is a gas-chambered needle-less device for IM delivery of epinephrine. Magnetic resonance imaging scans of healthy male and female thighs showed that the mean delivery depth was 30.1 ± 5.8 mm (range, 20.2–45.6 mm).⁷ This clearly shows that with a high-pressure needle-less device, epinephrine can be delivered pass the fascia into the IM tissue. In addition, the skin to muscle distance was far greater than the needle of any epinephrine autoinjector currently on the market. These data clearly establish the proof of concept that needle penetration of fascia is not *a sine qua non* for IM delivery of epinephrine. The data also show that propulsive force is a crucial factor in determining depth of penetration and is sufficient alone to produce facial puncture.

Compression also plays a role in determining delivery depth (Figure 1).⁸ To trigger an epinephrine autoinjector, pressure must be applied to the thigh. EpiPen requires 2 to 8 lb of pressure (9–35 N) and Emerade requires 3.4 to 3.8 lb of pressure (15–17 N) to trigger the devices. Both high-pressure and low-pressure trigger autoinjectors reduce the distance from skin to muscle. There are limited data on the degree of compression. One study mentions that 10% of compression is in the SQ tissue and 90% is in the muscle.⁹ Based on these data, compression is a factor, albeit small, that helps determine the depth of delivery of epinephrine.

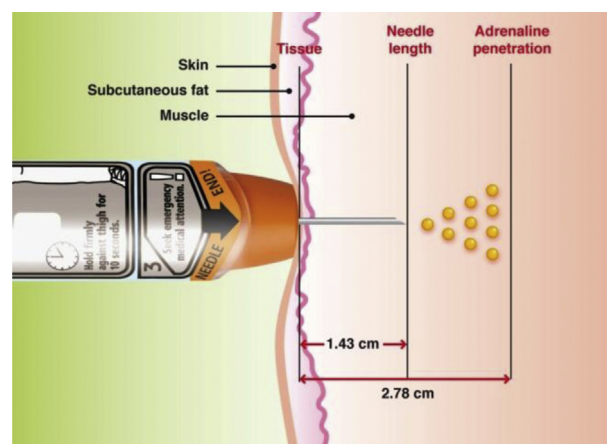


FIGURE 1. Compression of subcutaneous tissue by an autoinjector.

Let us agree for a moment that the fascia is impenetrable. If this is the case, then SQ injections of epinephrine should give smaller peak plasma concentration (C_{max}) compared to IM injections. However, a Duvauchelle et al¹⁰ study found that C_{max} after epinephrine injection by an autoinjector in overweight females receiving SQ injections was higher than in males with IM injections. There are a variety of factors that may have accounted for this observation. (See below for further discussion.) But one possibility is that the females received IM delivery. This cannot be conclusively ruled out.

Finally, the Duvauchelle et al study could also indicate that females may have different pharmacokinetic responses to epinephrine injection than males. We stated that “findings suggest that there may be other factors such as hormonal influences affecting the pharmacokinetics of this drug.” This statement should not be taken as dogma but as a call for more research in gender differences in bioavailability. In their critique, Dreborg and Kim stated: “Lastly, Song claims that estrogens may influence the pharmacokinetics of epinephrine when assessed in these studies that span several minutes only. We cannot rationalize how estrogen would impact epinephrine levels in such studies. We could not find any evidence in the medical literature to support this idea.” On the contrary, however, there is support for this possibility in the published peer-reviewed literature. Lenders et al¹¹ investigated the differences between hypertensive men and women to incremental IV doses of exogenous epinephrine. The venous plasma epinephrine levels in both genders increased, but the mean increase in males was nearly twice that of females. The authors state that estrogen “may” have a role in catecholamine metabolism and epinephrine clearance maybe different between genders. Furthermore, the effect of gender on the adrenergic system regarding both humoral and neural responses, including the metabolism of epinephrine, is well established and has been reviewed in detail.¹² Thus, we do not find it farfetched that baseline levels of circulating sex hormones could affect the catabolism/clearance of epinephrine. Certainly, this has been demonstrated clearly in relation to numerous other drugs including theophylline, metoprolol, and others.¹³

In conclusion, we again appreciate Dreborg and Kim’s comments. They are well taken. We can see how they reached their conclusions based on the excellent work of Diacono

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