

## Clinical Communications

### The deep fascia of the thigh forms an impenetrable barrier to fluid injected subcutaneously by autoinjectors

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#### Clinical Implications

- Fluid injected from epinephrine autoinjectors into subcutaneous tissue is prevented from penetrating into the muscle by the deep fascia of the thigh. Intramuscular injection will not occur during firing of an autoinjector if the needle tip is in the subcutaneous tissue.

#### TO THE EDITOR:

Epinephrine for self-administration in anaphylaxis should be administered intramuscularly rather than subcutaneously,<sup>1-3</sup> but in an increasing proportion of the population, epinephrine autoinjector (EAI) needles are shorter than the skin to muscle depth (STMD).<sup>4,5</sup> The aim of this study was to investigate claims that intramuscular injection from EAI may be possible even when the needle length is less than the STMD.<sup>6-8</sup>

We studied 4 EAI devices currently available in Europe (EpiPen [Meda Pharma, Bishop's Stortford, UK], Anapen [Lincoln Medical, Salsbury, UK], JEXT [ALK-Abello, Reading, UK], and Emerade [iMed Systems Ltd., London, UK]). Dispersal of injected fluid was traced by replacing the epinephrine in each device with a dye marker (1.0 g/L brilliant blue). Windows cut in the external casing of EAIs allowed movement of the plunger during firing to be recorded at 240 frames/s. Three separate data points were collected for each test variable, and for plunger velocity measurements medians compared using the Mann-Whitney *U* test.

Injections of 0.3 mL were made from 0.3 mg EAI at 21°C into 3 surrogate human tissue models.<sup>6-8</sup> In the first model, 2 cm diameter porcine tissue cylindrical blocks were cut from Berkshire pig hind legs obtained from a local abattoir (processed within 24 hours of death and re-equilibrated at 39°C). As the scalding of slaughtered pig skin in water at 60°C for 6 minutes was used in the abattoir to dehair pig carcasses, a second model using 12-week anesthetized and euthanized Hampshire piglets were also studied to ensure that the scalding process had not affected the dispersion of dye through subcutaneous tissue. The experiments were performed on piglets rather than adult pigs as the latter were too large to be handled in the animal house facility. Use of piglets was technically challenging, as autoinjectors had to be fired into the posterior neck rather than thighs, the only part of the body where the subcutaneous tissue was thick enough (10-30 mm) to allow comparative subcutaneous and intramuscular injections. In the third model, 10% ballistic gelatin was cast by pouring melted gelatin into 2 cm diameter steel cylinders or clear plastic boxes 7 × 7 × 3.5 cm<sup>3</sup>, before allowing it to set for 48 hours at 4°C. A sheepskin surface proved

TABLE I. Fluid jet velocity ejected into porcine tissue from epinephrine autoinjectors

Autoinjector brand (µg)	Needle projection (mm)	Median (range) jet velocity to 95% ejection (m/s)	Median (range) injection time (ms)
EpiPen 300	13	20.2 (20.2-21.8)	110 (110-110)
JEXT 300	13	18.8 (16.5-18.8)*	120 (120-130)
Emerade 300	21	21.0 (18.4-21.6)	170 (160-200)*
Anapen 300	8	4.1 (3.7-4.7)*	1500 (1300-6000)*

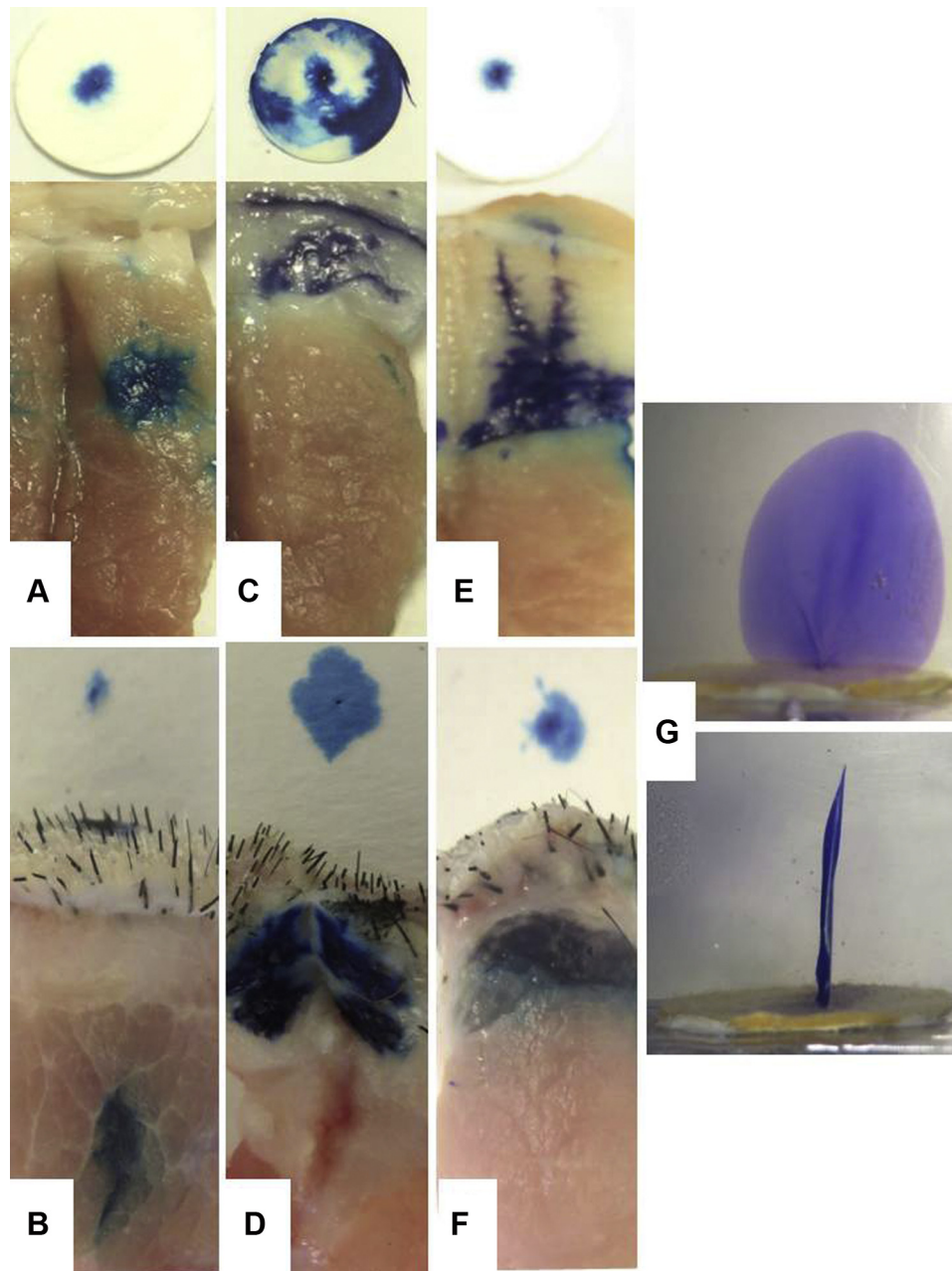
Needle projection was measured from where the needle protruded from the plastic casing to the proximal edge of the needle lumen. Fluid jet velocity through the EAI at 21°C was determined by calculating the [distance moved by the plunger]/[injection time] × [plunger cross-sectional area]/[needle lumen area]. Injection time is from start to finish of the plunger movement. n = 3.

\*Mann-Whitney *U* test *P* value <.05 compared with EpiPen 300.

necessary to prevent leakage of injected fluid back to the surface. For both the Berkshire pig tissue and ballistic gelatin experiments, EAI and tissue blocks were held in place within a specially built clamp with the camera mounted a fixed distance from and perpendicular to the mid-point of the plunger transit. For experiments using Hampshire piglets, injections were made directly into the animals and injection sites then dissected to reveal the dispersion of the dye. In all experiments, EAIs were held *in situ* for 10 seconds after firing to allow time for the dye to disperse into the tissue and reduce leakage back along the needle track. Blocks were then immediately retrieved from the test chamber and photographed. Each condition was repeated on 5 different occasions to confirm consistency of results.

With the EAI at 21°C, the original epinephrine and replacement dye solutions were discharged at the same rate into air. The velocity of injection of fluid into the pig tissue was similar from EpiPen, JEXT, and Emerade, but substantially lower from Anapen. Apart from Anapen, all EAIs discharged their contents within 200 milliseconds (Table I). Dye injected from all EAIs tracked from the needle orifice through the tissues along paths of least resistance. Dye injected into the muscle was propelled along the muscle fibers (Figure 1, *a* [Berkshire pig] and *b* [Hampshire piglet]). In contrast, dye injected subcutaneously was prevented from reaching the underlying muscle by the deep fascia (Figure 1, *c*, *e* [Berkshire pig] and *d*, *f* [Hampshire piglet]). Using an EpiPen 150 (the EAI with highest jet momentum) and removing all the tissues superficial to the deep fascia, no dye penetrated even the superficial layers of the deep fascia when fired with an air gap of ≈ 1 mm from the needle tip. This indicated that the momentum of the jet emerging from the needle was insufficient to cause intramuscular dispersal after subcutaneous injection and also that it was not binding of brilliant blue to the proteins in the subcutaneous tissue that prevented the dye from entering the muscle (data not shown).

Injection into 10% ballistic gelatin at 4°C was completed by EpiPen in 120 milliseconds and by Anapen in 1500 milliseconds. After firing the Anapen autoinjector, fracture cleavage of the gelatin propagated as an expanding disk centered on the needle (Figure 1, *g*). Despite the low jet velocity, in gelatin dye flows well beyond the Anapen needle tip, as it did for the other EAIs.



**FIGURE 1.** Distribution of brilliant blue dye injected from autoinjectors into pig tissue and ballistic gelatin. The upper panels show injections into a Berkshire leg of pork obtained from an abattoir and processed within 24 hours (a, intramuscular injection; c, subcutaneous injection; e, injection at the subcutaneous-muscle junction), and the lower panels into freshly euthanized Hampshire piglets (b, intramuscular injection; d, subcutaneous injection; f, injection at the subcutaneous-muscle junction). Both preparations were at body temperature at the time of injection. Blotting paper demonstrates leakage of dye back along needle track after withdrawing the device 10 seconds after injection. The right panel (g) shows two views of injection by Anapen into 10% ballistic gelatin block at 4°C where dye extends well beyond the tip of the needle along a fracture plane.

Our experiments clearly demonstrate that dispersal of dye into animal tissue is modified by its complex structure. Injection into ballistic gelatin is thus a poor model for studying movement of fluid through tissues, as it fails to take into account the disruption to fluid movement by the deep fascia.<sup>7,8</sup> We show that the deep fascia of the thigh (*fascia lata* in humans) prevents fluid traveling from the subcutaneous tissue into the underlying

muscle.<sup>9</sup> Where injections are made directly into the porcine muscle, our results are consistent with those of Song et al,<sup>6</sup> who found that dye travels beyond the length of the EAI needle. It should however be noted that the subcutaneous tissue depth of Song et al's pig thighs were on average only 7 mm, and thus EAI needles were long enough to penetrate into the muscle in all their experiments (personal communication). Furthermore, Song et al

defined STMD as the “distance from the surface of the skin to the methylene blue/epinephrine mixture” and not as the distance between the surface of the skin and the fascia at the interface between the subcutaneous tissue and the muscle. Thus, the intramuscular injections observed in their study are not because of propulsion of fluid through the subcutaneous tissue or because of compression of the subcutaneous tissue, but rather because of the thin skin STMD in their porcine tissue model.

In summary, we clearly show that if the EAI needle orifice only penetrates into the subcutaneous tissue, fluid is prevented from entering the muscle by the intervening deep fascia. Where the STMD is thicker, as in obese patients, intramuscular injection may not be achieved and either a more distal location,<sup>4</sup> or use of an autoinjector with a longer needle length (Emerade) might be considered. Although the intramuscular rather than the subcutaneous route is generally recommended for administration of epinephrine in anaphylaxis, there are no studies that directly compare the clinical effectiveness of the two routes in the treatment of anaphylaxis; epinephrine through either route helps. Thus, the EAI remains the first-line treatment for anaphylaxis regardless of obesity.

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