Fluoroscopic Assessment of Percutaneous Cannula Penetration Depth

Bruce Roberts, BS; Christopher J. Rini, MS; Nicholas Oberlander; Ronald J. Pettis, PhD
BD Technologies and Innovation
Research Triangle Park, NC, USA

Background and Aims

Self-administered injection therapy is common practice for diabetes therapy and continues to increase in prevalence, with subcutaneous tissue being the preferred administration site for syringes, pen injectors, and insulin pump systems. Ideally, these devices should enable consistent and reproducible SC delivery regardless of variation in tissue morphology, injection location, or delivery technique. Previous assessments of delivery devices focused on physical measurements of the patient end length (PEL) of the insertion cannula and standard in vivo functional testing. The application of imaging techniques to further elucidate insulin delivery device in vivo function has proven increasingly valuable as new devices are developed. Fluoroscopic imaging enables direct observation of phenomenon such as tissue compression and tenting during insertion/injection, including in situ visualization and characterization of injectate depositions. A desired extension of this technique was measurement of cannula penetration depth (CPD), however inhomogeneous depot dispersion precludes consistent visualization of the entire cannula length [Figure 1]. Therefore it was necessary to develop a method to accurately visualize and measure cannula penetration depth post injection.

Animal Model

In vivo work conducted for this study was done on the Yorkshire swine model. Live animals provide the best model for evaluating injection dynamics and biomechanics; to date, no in vitro mechanical model exists that can simulate the complexities of an intact in vivo integumentary system. Swine are the ideal species for evaluation of insulin infusion/injection products and are the preferred models in wound healing and plastic surgery research due to the similarities of their skin to human skin tissue.

- In vivo swine skin has been noted to better mimic live human skin than cadaver human skin is studies conducted by Ranamukhaarachchi et al (1).
- Swine are tight-skinned animals like humans, and the presence of a dermal collagenous network makes their skin elasticity more like humans than other mammal models (2) (3).
- Swine have similar structural and compositional dermal and subcutaneous (SC) tissue characteristics (pigmentation, hair paucity, skin thickness, dermal to epidermal ratio, adipocyte size and layering, compliance, drainage, absorption, and resistance) (4) (3) (5) (6) (7) and biological variables (breathing, movement, tissue variability, similar vasculature patterns) (3) (5) that devices encounter in use.
- A difference between swine and human SC structure is the presence of the panniculus carnosus (8), a layer(s) of striated muscle in the SC tissue that contributes to skin movement (twitch reflex). The flank provides a diminished panniculus carnosus while still providing a SC depth similar to humans.

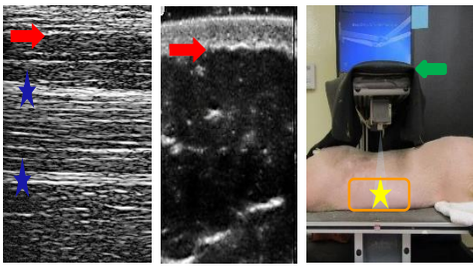

Figure 2. Above left is an ultrasound of Yorkshire swine skin displaying the structure of the subcutaneous (SC) tissue space (red arrow indicates the boarder between the dermis and the SC, purple stars indicate the panniculus carnosus muscles). Above middle is an ultrasound of human skin displaying the structure of the SC tissue space (red arrow indicates the boarder between the dermis and the SC). Above right is an image of a Yorkshire swine in sternal recumbency on the Glenbrook Technologies- LabScope™ C-arm fluoroscope with the lead curtain shielding (green arrow) retracted for image clarity. The x-ray beam path is indicated by the transparent white triangle and the injection site is denoted by the yellow star. In this configuration the injection would be administered perpendicular to the surface of the skin and the beam path. The orange rectangle indicates the zone on the Yorkshire swine flank where we conduct our injection trials. Depending on the study as many as 4 injections can be administered to a swine in one experimental day.

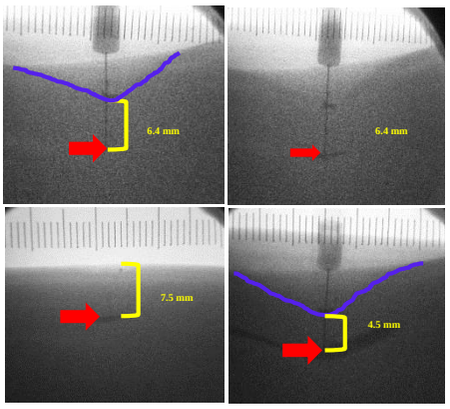

Figure 1. Above are fluoroscopic images of the subcutaneous tissue space of a Yorkshire swine. A: Image immediately following insertion of the cannula into the tissue. B: Image of a small volume of injectate (20 µl) delivered to the tissue. C: Image of the small volume (20 µl) deposition following removal of the delivery device. D: Image of a large deposition of injectate (300 µl) delivered to the tissue. In all images the purple line denotes the surface of the skin that is interfacing with the hub of the delivery device, the red arrow indicates the tip of the deliver cannula (panel A) or the top of the injectate deposition (panels B, C, and D), the yellow bracket denotes the depth measurement which is in mm. Note that during delivery (panels A and B) the delivery device is compressing the tissue compared to he non compressed tissue in panel C (6.4 vs. 7.5 mm depth). Also note that the expansion of the large volume injectate deposition in panel D results in an inappropriately shallow depth measurement.

Method

Cannula penetration depth was measured for 5 different 6mm PEL syringe devices (n=50/syringe).

- 20µl of contrast agent (350 mg/ml Iohexol) was deposited in the SC of the flank of a 30-40 kg anesthetized female Yorkshire swine with each test article. The skin thickness and underlying muscular support on the flank of this age Yorkshire swine closely mimics the average human abdomen [Figure 2]. Animals were positioned under the fluoroscope so that the cannula insertion was perpendicular (90°) to the beam path [Figure 2].
- The 20µl deposition created a visible point marker in the tissue [Figure 4] representing the tip position of the cannula during fluid administration.
- All fluoroscope images included a leaded mm scale ruler for measurement calibration [Figure 4].
- Mean cannula penetration depths were tested against the traditionally expected value of 6mm (the design length for the patient end length cannula).

Figure 3. Top panel depicts prototype syringe evaluated in this study. Bottom panel is an enlargement of the prototype hub design of the syringe. Multiple Comparisons

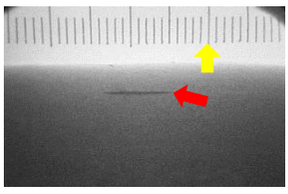

Figure 4. Fluoroscopic image of a small volume deposition in the subcutaneous tissue space of a Yorkshire swine (red arrow). Included in this image is a millimeter scale (yellow arrow) used for calibration of measurements. This calibration scale is included in all images where measurements are made.

Results

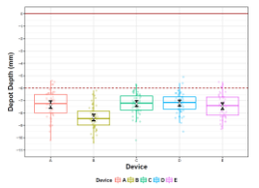

Figure 5. Box plot of deposition depths by device. Means are represented by open circles and error bars are SEM. Median value is the horizontal bar and the box represents the interquartile range. Vertical lines represent the range of the data.

Device	Mean +/- SEM
A	7.32 +/- 0.15
B	8.38 +/- 0.13
C	7.24 +/- 0.12
D	7.21 +/- 0.12
E	7.45 +/- 0.13

Table 1. Table of mean deposition depths in mm ± SEM (n=50/device).

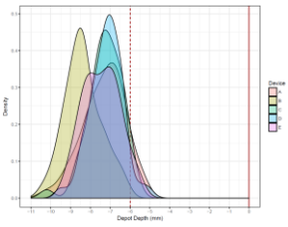

Figure 6. To the left are density plots of deposition depths by device. Note the dashed red line indicates the PEL of all devices and the traditionally expected value for the deposition depth. All devices produced depositions significantly deeper than the PEL length of 6mm (p<0.0001).

Conclusions and Future Directions

- The swine model flank provides sufficient injection surface area to allow testing of multiple devices at clinically relevant dosing rates and volumes without causing significant discomfort / physical impairment to the animal.
- Measuring CPD after device removal eliminates the influence of compressive forces placed on tissue at insertion site by the delivery device that may result in artificially shallow measurements [Figure 1].
- The point depositions created with the method were readily identifiable by fluoroscopy enabling the accurate in vivo measurement of cannula penetration and performance characterization of SC delivery devices.
- Devices with identical 6mm PEL cannulas produced different cannula penetration depths, demonstrating that patient end length of the device alone is not a reliable predictor of injection depth.
- Cannula penetration depth greater than cannula patient end length of the device may be due to differences in localized tissue compression created by device design and/or technique during the injection procedure.
- Other factors influencing cannula penetration depth should be further examined to increase injection consistency and reproducibility.

References

[1]**Ranamukhaarachchi.** *A micromechanical comparison of human porcine skin before and after preservation by freezing for medical device development.* s.l. : Nature.com Science Reports, 2016. [2] *Insulin depot formation in subcutaneous tissue.* **Jockel, JP.** 1, Jan 1, 2013, J Diabetes Sci Technol, Vol. 7, pp. 227-37. [3] *Biomechanics of the Sensor-TissueInterface-Effects of Motion, Pressure, and Design on Sensor Performance and the Foreign Body Response-Part I: Theoretical Framework.* **Helton, K.** 3, May 2011, JDST, Vol. 5, pp. 632-646. [4] *Of Pigs & Research.* **Douglas.** 1971. [5] *Swine as models in biomedical research and toxicology testing.* **Swindle, M, et al.** 2, 2012, Veterinary Pathology, Vol. 49, pp. 344-356. [6] *Spatial distribution of soluble insulin in pig SC tissue: Effect of needle length, injection speed & injected volume.* **Thomsen M, et al.** 2015, European J Pharm Sci. [7]. *Pharmacokinetics of the rapid-acting insulin analog, insulin aspart, in rats, dogs, and pigs, and pharmacodynamics of insulin aspart in pigs.* **Plum A, Agerso H, Andersen L.** 2, 2000, Drug Metab Dispos, Vol. 28, pp. 155-160. [8] *SC administration of biotherapeutics: Current experience in animals models.* **MacDonald, Zepeda, et al.** 4, 2010, Current Opinion in Molecular Therapeutics, Vol. 12, pp. 461-470. [9] *Initial drug depot formation in subcutaneous tissue.* **J, Leubenberger.** 2013. ATTD. [10] *Influence of hypodermic needle dimensions on subcutaneous injection delivery-a pig study of injection deposition evaluated by CT scanning, histology and backflow.* **Juul KA, et al.** 2012, Skin Research and Technology, Vol. 18, pp. 447-455. [11] *Porcine model to evaluate local tissue tolerability associated with subcutaneous delivery of protein.* **Kang DW, et al.** 2013, Journal of Pharmacological and Toxicological Methods, Vol. 67, pp. 140-147. [12] *Comparison of the pharmacokinetics of three concentrations of insulin aspart during continuous subcutaneous insulin infusion (CSII) in a pi model.* **Petersen SB, Nielson FS, et al.** 2, 2013, J Pharm Pharmacol, Vol. 65, pp. 230-235. [13] *Mechanistic determinants of biotherapeutics absorption following SC administration.* **Richter WF, et al.** 3, 2012, AAPSJ, Vol. 14, pp. 559-570. [14] *Bread and age affect baseline immune traits cortisol and performance in growing pigs.* **Rutherland MA, Rodriguge-Zas SL, et al.** 2005, J of Animal Science, Vol. 83, pp. 2087-2095. [15] *Visualization of subcutaneous insulin injections by x-ray computed tomography.* **Thomsen M, et al.** 21, 2012, Phys Med Biol, Vol. 57, pp. 7191-7203. [16] *The microvascular in cutaneous wound healing in the female red Duroc pig is similar to that in human hypertrophic scars and different from that in the female Yorkshire pig.* **Xie Y, Zhu KQ, et al.** 3, 2007, J. Burn Care Res, Vol. 28, pp. 500-506.