Depot visualization and tissue back-pressure measurement of large volume subcutaneous injections

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Abstract

Introduction

Subcutaneous (SC) injection is a route of administration positioning drug formulations in the hypodermis and offering numerous advantages for the patients (1, 2). Such injections induce a tissue backpressure which opposes these injections (3). This backpressure is dependent of the formulation spreading in the hypodermis, which is controlled by mechanical phenomena.

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The identification of those mechanical phenomena and of the factors impacting backpressure during large volume SC injections is needed, since backpressure prediction is required for drug delivery devices dimensioning. Those devices must overcome backpressure to ensure the total administration of the targeted formulation volumes (3). Such identification should play a part in enabling patients to self-administrate subcutaneously new active ingredients, such as monoclonal antibodies, which must be associated to larger volumes for stability, and delivery reasons (6).

Also, tolerable injection condition limits for SC injections of large volumes are unknown, although authors considered that backpressure at the injection point should be a great indicator of how tolerable an injection is (7).

There is thus a need for better understanding skin deformation, formulation diffusion, and tolerable injection condition limits for SC injections of large volumes.

To determine them, we propose first to estimate upper tolerable injection rates for given

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formulation viscosities. We propose then to carry out SC injections of placebos representative of drug formulations (1) in the animal anatomical zone presenting the most similar hypodermis compared to human abdomen (8), measuring backpressure and visualizing formulation depot post-injection thanks to contrast absorption X-ray microtomography.

Methods

Placebos and tissue samples

Two types of placebos were used.

To determine tolerable injection condition limits, a hyaluronan dermal filler (Stylage Hydro®, Vivacy Laboratories) diluted at 20% v/v in NaCl 0.9% has been chosen (2).

To carry out formulation depot imaging post-injection, solutions with viscosities of 1, 10, 20 and 100 mPa.s and a Newtonian rheological behavior were used. To obtain them, dextran 40 kDa (Apollo Scientific, UK) was diluted at different concentrations in a contrast solution (Iomeron®, Bracco Imaging, Italy).

Both previous placebo types were injected at room temperature in fresh *ex vivo* belly flank pork samples (containing skin, hypodermis, and deep muscle in their thickness).

Experimental set-up and backpressure measurement

A device containing a push-syringe, a syringe, a tubing and a catheter was used to carry out the SC injections. A catheter (24G) was inserted in the tissue sample at 90◦ to the skin surface and at a depth of 9 mm, thanks to a specific support glued to the skin surface. To measure the pressure during SC injection according to time, an in-line pressure sensor was positioned between the syringe and the tubing.

Injection conditions

The maximal tolerable backpressure during a SC injection was determined reproducing as much as possible injections which caused tolerability issues for patients (2.5 mL of hyaluronan placebo at 15 mL/min (2)).

The maximal injection rate associated to each viscosity of dextran/contrast agent placebos was then determined to not induce larger backpressures than maximal tolerable value, thanks to relations found by Allmendinger et al. (1). The lower injection rate was chosen as the lower injection rate preference of some individuals within clinical trials (_˜0.3 mL/min). The same volume, sufficient to reach the backpressure stabilization for each viscosity and injection rate combination was used for all injections.

X-ray computed micro-tomography

Two absorption contrast X-ray micro-tomography scans were carried out. One with the radio-opaque cannula already inserted for each sample before injection. Another after the SC injection. Each scan required an acquisition duration of 35 minutes with a Phoenix Nanotom S® (GE and Inspection Technologies). Cubic voxels of side 30 μm were reached. Each scan was then reconstructed with 3D Slicer.

Analysis

To determine the hypodermis thickness and the location of the injection point relative to hypodermis substructures and deep muscles, the segmentation of the tissue layers was carried out with a thresholding segmentation, after applying a 3D median filter. The segmentation of the formulation depots was also carried out thanks to a Chan-Vese segmentation, to visualize and measure depots, and to quantify the amount of formulation positioned in each

hypodermis substructure. Orthographic projections were finally generated to study formulation depot homogeneity according to locations in the depots.

Results

Experimental study is still on-going; first results show that the formulation with lower viscosity was positioned in membranous hypodermis substructures (septas) post-injection, as for smaller volumes of similar viscosity (5). Hypodermis permeability was also anisotropic and impacted by the presence of specific hypodermis substructures.

Discussion and conclusion

It is thus expected that the nature of the hypodermis substructures in which the formulation is positioned post-injection and the mechanical phenomena involved in the formulation spreading should be identified for all the injection conditions studied here, representative of large volume SC injections. Focus will also be put on relations between backpressure reached, hypodermis properties (thickness, substructures), injection point, viscosity, and injection rate. Such results will facilitate the creation of numerical models predicting the backpressures generated by SC injections of large volumes for the different injection conditions tolerated by patients.

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