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Understanding Subcutaneous Tissue Pressure for Engineering Injection Devices for Large-Volume Protein Delivery

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ABSTRACT

Subcutaneous injection allows for self-administration of monoclonal antibodies using prefilled syringes, autoinjectors, and on-body injector devices. However, subcutaneous injections are typically limited to 1 mL due to concerns of injection pain from volume, viscosity, and formulation characteristics. Back pressure can serve as an indicator for changes in subcutaneous mechanical properties leading to pain during injection. The purpose of this study was to investigate subcutaneous pressures and injection site reactions as a function of injection volume and flow rate. A pressure sensor in the fluid path recorded subcutaneous pressures in the abdomen of Yorkshire swine. The subcutaneous tissue accommodates large-volume injections and with little back pressure as long as low flow rates are used. A 1 mL injection in 10 seconds (360 mL/h flow rate) generated a pressure of 24.0 ± 3.4 kPa, whereas 10 mL delivered in 10 minutes (60 mL/h flow rate) generated a pressure of 7.4 ± 7.8 kPa. After the injection, the pressure decays to 0 over several seconds. The subcutaneous pressures and mechanical strain increased with increasing flow rate but not increasing dose volume. These data are useful for the design of injection devices to mitigate back pressure and pain during subcutaneous large-volume injection.

Introduction

Subcutaneous injection offers several advantages over intravenous delivery, particularly for monoclonal antibodies, such as facilitating at-home patient self-administration, use of ambulatory devices, decreased incidence of infusion reactions and errors during administration, reduced health care costs, and a lower plasma maximum concentration (C_{max}) relative to intravenous infusions.[1-4] Self-administration of subcutaneous injection volumes up to 1 mL is clinically and commercially acceptable for therapeutic monoclonal antibody products and small molecules. Several commercial subcutaneous products up to 1 mL are available, including Enbrel (Amgen, Thousand Oaks, CA), Humira (AbbVie, North Chicago, IL), Simponi (Janssen Biotech, Horsham, PA), and Stelaris (Janssen Biotech).[5-9] When the therapeutic dose can be formulated in ≤1 mL, prefilled syringes and autoinjectors typically serve as the preferred delivery systems for subcutaneous self-administration.[6,10]

To limit the injection volume to 1 mL, monoclonal antibody formulations often need to be formulated at high concentrations at ≥100 mg/mL. High-concentration liquid monoclonal antibody formulations can present problems in manufacturing and delivery because of high viscosities, limitations of protein solubility, aggregation, and protein stability under long-term storage.[11-13] At the current standard of care, small molecules and monoclonal antibodies may either be delivered via multiple injections of up to 1 mL or one large-volume injection when the required dosing exceeds 1 mL. The requirement of multiple injections raises concerns of patient noncompliance and inconvenient dosing. For injection volumes >1 mL, there are concerns of increased pain upon injection, high subcutaneous back pressure, site leakage, and injection site reactions.[14-21]

Studies investigating subcutaneous rehydration and subcutaneous immunoglobulin replacement therapy have shown that the subcutaneous tissue can accommodate volumes >1 mL with good tolerability.[22-27] Hizentra (CSL Behring, Kankakee, IL), Gammunex-C (Grifols Therapeutics, Research Triangle Park, NC), and Gammagard Liquid (Baxter, Westlake Village, CA) are commercially available immunoglobulin replacement products in the United States.[28] Per the Hizentra prescribing information, up to 25 mL infusion volume may be injected up to a maximum flow rate

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of 25 mL/h per site as tolerated by the patient. Qualitative measurements or percent incidence of pain upon injection, swelling, and soreness is typically reported in immunoglobulin replacement therapy.[23,29-31] Furthermore, quantitative pain measurement through the use of visual analog scale or other pain scales can also be found, which further supports the use of large-volume injection.[32-34] Ambulatory, reusable syringe pumps with tethered subcutaneous insertion sets are typically used for subcutaneous immunoglobulin replacement therapy.[33-35]

Self-administration of subcutaneous injection volumes >1 mL can be delivered by disposable large-volume syringes, large-volume (2.25 mL) prefilled syringes, large-volume autoinjectors, and on-body injectors.[36] Subcutaneous back pressure is one of the parameters that can serve as an indicator for the changes in the mechanical properties of the skin leading to pain during injection. The subcutaneous tissue is comprised of the extracellular matrix and the interstitial fluid. The extracellular matrix consists of collagen, hyaluronic acid, and chondroitin sulphate.[37] The interstitial fluid hydrostatic pressure is determined by the volume of interstitial fluid and the elasticity of the extracellular matrix, which affects the volume and rate of subcutaneous injections. Hyaluronidase can be coadministered or coformulated with monoclonal antibodies to facilitate large-volume injections. Hyaluronidase transiently degrades hyaluronic acid and can be used to decrease interstitial pressure during a subcutaneous injection.[17]

Previous reports of the effect of flow rate on subcutaneous back pressure are described in the literature.[17,18,20,38] However, there are no studies that have systematically investigated back pressures for a wide range of volumes and flow rates relevant for subcutaneous injection without the use of an absorption enhancer such as hyaluronidase. In addition, no subcutaneous back pressure measurements found in the literature compare large-volume subcutaneous delivery to a 1 mL delivery known to be clinically acceptable. It is also important to investigate the injection site reactions of large-volume subcutaneous delivery and to account for subcutaneous back pressure while designing large-volume delivery devices. Therefore, the aim of this study was to investigate the effects of injection volume and flow rate on subcutaneous pressure and injection site tolerability in a porcine model. Swine were selected as a model for human subcutaneous injections as an accepted skin surrogate model for humans because of the similarity in the thickness of the subcutaneous tissue.[39-41]

Materials and Methods

Injectate Preparation

Isotonic solutions were prepared to mimic low-viscosity monoclonal antibody formulations. The low-viscosity injectate was a phosphate-buffered saline solution comprising 185 mM sodium chloride and 5 mM dibasic sodium phosphate in water (pH 7). A high-viscosity solution was formulated and comprised 15.5% povidone (Plasdone C-30, International Specialty Products, Texas City, TX), 75 mM sodium chloride, 5 mM dibasic sodium phosphate in water (pH 7). Viscosity was measured at a shear rate of 1080/s using a MCR-301 torsional rheometer (Anton Paar, Graz, Austria) equipped with a CP-50 cone and plate apparatus. Both solutions were provided sterile for this study and the stability (appearance, osmolality, pH, and viscosity) was monitored throughout the study.

Equipment

A 25 G × ½-in Sureflo winged butterfly set (Terumo, Somerset, NJ) was connected to an in-line pressure sensor (Model PRESS-S-000; PendoTECH, Princeton, NJ). Each pressure sensor was tested by the vendor and passed a leak test to confirm integral assembly. The accuracy of each pressure sensor was also tested by the vendor and was required to be within 30 psi ± 2%. The pressure sensor has a narrow flow through path that allowed the phosphate-buffered saline to flow through the sensor and measurements be made in line to the butterfly set. The sensor was connected to a 21 in extension set (Baxter, Deerfield, IL) to add length to the fluid path. The extension set was connected to either a 10 mL (for injection volumes 1-5 mL) or 30 mL (for 10 mL injection volumes) plastic syringe (Becton Dickinson, Franklin Lakes, NJ). All components used a luer lock connection. A syringe pump (PHD Ultra; Harvard Apparatus, Holliston, MA) was used to deliver the injection by setting the syringe size, injection volume, and flow rate. The pump and pressure sensor were connected to a computer running LabView (National Instruments, Austin, TX) that collected time, pressure, and delivered volume data. Figure 1 depicts the equipment used in this study.

Animals Used in the Study

This study was conducted in compliance with the US Department of Agriculture's Animal Welfare Act (9 CFR Parts 1, 2, and 3). The Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, Washington, D.C.) was followed. The study was reviewed and received approval by the internal MedImmune Animal Working Group and by the external Contract Research Organization Institutional Animal Care and Use Committee. Domestic Yorkshire crossbred swine of approximately 18-19 weeks of age were received and acclimated to the site facility for about 10 days. The body weights at the start of the study were 68.5-75.0 kg. All animals were observed for morbidity, mortality, injury, and the availability of food and water twice daily for the duration of the study. Animals were provided enrichment throughout the study. Animals were fasted overnight before the injections. Animals were anesthetized and placed in supine position for the injections. Four injection sites per animal were marked on the abdomen with an indelible black marker before the injections and were approximately 10 cm apart. To accommodate the number of injections tested in the study while limiting the

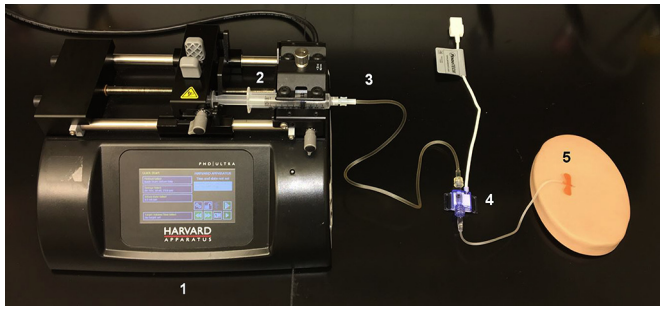

Figure 1. Schematic of the equipment used in the study. All fluid path lines were connected through the use of luer lock connections. (1) A Harvard Apparatus PhD Ultra syringe pump was used as the drive mechanism to deliver the injections to the subcutaneous tissue. The syringe pump was connected to a computer (not shown) running LabView that collected time, pressure, and volume data. (2) A 10 or 30 mL plastic syringe was filled with injectate. (3) A 21 in extension set was connected to the syringe to add length to the fluid path. (4) A pressure sensor was connected to the extension set. The pressure sensor contains a flow through path so that the pressure measurements could be made in-line to the fluid path. The pressure sensor was connected to the computer (not shown). (5) A 25G × ½-in winged butterfly set was connected to the distal end of the pressure sensor. The butterfly set is shown inserted into a skin mimic pad to illustrate the insertion of the needle. In this study, the butterfly set was inserted into the subcutaneous tissue for the injections.