Elucidating subcutaneous depot formation and release of the injectable anti-diabetics taspoglutide in rats using in vivo MRI

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Background – Subcutaneous injection is an established route of administration for pharmacological interventions. It is generally accepted that the ensuing drug uptake and availability is strongly governed by the drug's immediate fate at the injection site but the latter has largely remained unexplored (1). Here, we used in vivo MRI to address this question for the anti-diabetic agent taspoglutide with the aim of providing a mechanistic rationale for the complex pharmacokinetics observed for its sustained release formulation (SRF). Taspoglutide is an analogue of the human glucagon-like peptide-1 which advanced to Phase 3 clinical development for treatment of type 2 diabetes (2). Its sustained release formulation is a clear solution of the peptide that is designed to jelly and form a depot upon subcutaneous injection. In this study, different injection conditions were compared for their performance in a rat model of type 2 diabetes. MRI yielded quantitative estimates of depot formation and dissolution that were then related to the pharmacokinetics of taspoglutide.

Methods – Male ZDF rats (~350g) were used as a model of type 2 diabetes. Morphology of the subcutaneous depot was quantitatively investigated in situ with MRI before, during the first 80 min., 23 h and 3-17 d after a single bolus of taspoglutide SRF administered into the nape. Four conditions were tested in 10 animals each: 100µL and 200µL taspoglutide SRF were administered with two different prefilled injection devices (A and B). MRI was performed on a Bruker Biospec 4.7T/40cm scanner equipped with a body coil and receive-only head coil. Sagittal high-resolution RARE-32 images were acquired with TE_{eff}/TR=100/9400ms, $(26mm)^2$ field of view, 30 slices of 0.5mm thickness, 256x192 matrix, fat suppression, 8 averages, and 7.5min/volume scan time. Pharmacokinetics was assessed by measuring drug exposure with LC-MS/MS in plasma obtained from sublingual blood sampling after each MRI examination.

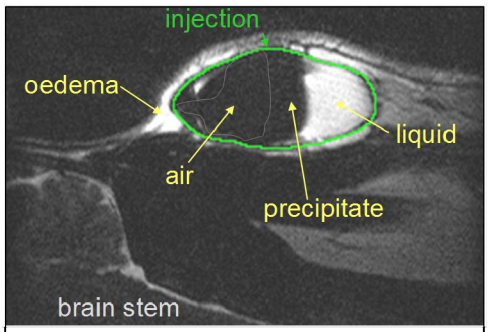

Fig. 1: Subcutaneous depot of taspoglutide

Results and Discussion – Subcutaneous depots formed after injection of taspoglutide SRF consisted of a liquid phase, gel and co-injected air, and were surrounded by an oedema in the host tissue (Fig. 1). Depot size remained fairly constant over the first 80 minutes but shrank subsequently over time with the most prominent changes occurring in the first 24 hours. Depot volumes upon injection with device B tended to be larger than with device A (132±10µL and 261±18µL (A) versus 156±10µL and 287±16 µL (B); $p<0.08$). Marked local reduction in signal intensity observed within the depots visualised in situ the jellying process that is supposed to impart the formulation's slow release properties. Depots formed after injection of 100 µL taspoglutide SRF jellied significantly faster than 200 µL depots (13±3min versus 33±7min (A) and 13±1min versus 29±5min (B); $p<0.01$) (Fig. 2). The drug exposure-time profiles were different for device A and B: C_{max} was 63ng/mL (A) versus 71ng/mL (B), and 72ng/mL (A) versus 96ng/mL (B) for the 100µL and 200µL injections, respectively. The corresponding values for $AUC_{(0\text{-}408h)}$ were 10400, 15300, 17400, and 18600ng·h/mL, respectively.

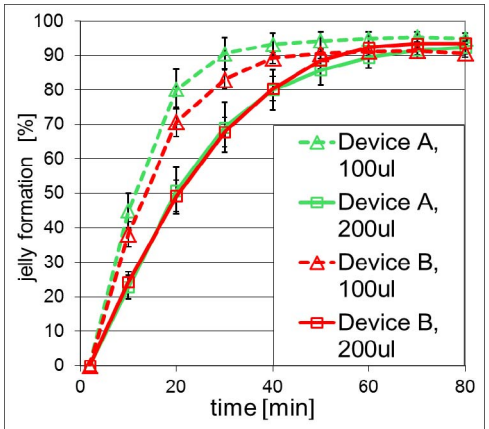

Fig. 2: Sustained-release depot formation

Conclusions – MRI was successfully used to quantitatively characterize size and composition of the subcutaneous depots over time. Plasma exposure of taspoglutide was 1.1-1.5fold higher upon subcutaneous injection with device B as compared to device A, and drug exposure was less than dose-proportional. Correlation of pharmacokinetics and structural MRI data suggest that depot size is driving exposure, thus providing a mechanistic rationale for the differences between the two injection devices and the non-dose-proportional exposure observed in this study.

References

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2. Dong JZ et al. Discovery and characterization of taspoglutide, a novel analogue of human glucagon-like peptide-1, engineered for sustained therapeutic activity in type 2 diabetes. Diab Obes Metabol. 2011; 13:19-25.