Assessment of the Tissue Hydraulic Resistance at the Site of Subcutaneous Insulin Infusion and Its Relation to Subcutaneous Insulin Absorption (HYDRA-02)

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Objective: The main goal of the study was to assess the strength of the relationship between the extent of insulin absorption and tissue flow resistance (i.e., the resistance exerted by the tissue on the infused insulin solution) during prolonged use of an insulin infusion site.

Methods: Twenty-two type 1 diabetes patients underwent an oral glucose tolerance test (OGTT) at the start of the 1st (Day 0), at the start of the 7th (Day 6), and last day of prolonged infusion site use (up to 14 days). During each OGTT, insulin pharmacokinetics (PK) and glucose pharmacodynamics (PD) were measured on delivery of a bolus of rapid-acting insulin. PK responses were regressed on the tissue flow resistance (TFR), which was assessed daily during infusion site use by measuring the pressure required to infuse boluses of 0.9% normal saline. The last day of infusion site use occurred once TFR exceeded a value of 20 kPa*s/µL.

Results: Twenty-six subjects with type 1 diabetes were invited to take part in the study. Of these, 2 were excluded due to screening errors and 2 were discontinued from the study due to venous access problems. The 22 subjects who completed the study (8 women and 14 men) had a mean ±SD age of 39.7 ± 13.3 years (range 21-60 years) and a mean ± SD body mass index of 26.9 ± 3.9 kg/m^2 (range 22.1-35.3 kg/m^2). Their mean ± SD diabetes duration was 23.8 ± 11.7 years (range 8-49 years), and their mean ± SD HbA1c level was 53 ± 6 mmol/mol (7.0 ± 0.6%; range 41-65 mmol/mol [5.9-8.1%]; normal range 23-41 mmol/mol [4.3-5.9%]). We observed that the mean±SE area under the plasma insulin curves ($AUC_{INSULIN}$) was substantially higher during the OGTTs on Day 0 and Day 7 than during the OGTTs performed after a mean ±SD infusion site usage time of 10.9 ± 1.7 days (Day 0: 25860 ±2982 pMol*min; Day 7: 21805 ±2980 pMol*min vs Last Day: 11338 ±1729 pMol*min; $p<0.001$). Furthermore, the geometric mean */geometric standard deviation TFR level at the insulin infusion site progressively increased with usage duration (Day 0: 0.58 */5.55 kPa*s/µL vs Day 7: 11.44 */2.62 kPa*s/µL vs Last Day: 46.18 */1.90 kPa*s/µL; $p<0.001$). Additionally, linear mixed effects model analysis of insulin and TFR data showed that TFR is strongly correlated with the $AUC_{INSULIN}$. The conditional coefficient of determination (R^2_C) was 0.87, indicating that TFR can predict 87% of the variation in $AUC_{INSULIN}$ within subjects.

Conclusions: Due to the strong relationship between TFR and insulin absorption efficiency, monitoring TFR may enable estimation of the current insulin absorption efficiency at an individual infusion site. This, in turn, may allow determination of the optimal wear time of an insulin infusion cannula.