Evaluation of the Hydraulic Tissue Resistance at the Site of Subcutaneous Insulin Infusion and Determination of Its Relationship to Insulin Absorption and Duration of Use of the Infusion Site (HYDRA-01)

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Objective: The goal of the study was to assess the resistance exerted by the tissue upon the insulin solution entering the tissue at the administration site (tissue flow resistance; TFR) and determine its relationship to the ability of the tissue to absorb the administered insulin.

Methods: Ten people with type 1 diabetes used an insulin infusion site for a prolonged period (up to 13 days). The TFR was assessed daily by measuring the pressure required to infuse boluses of insulin diluting medium. To assess the efficiency of insulin absorption from the subcutaneous infusion site, the subjects underwent a 75g-oral glucose tolerance tests (OGTT) at the beginning of infusion site use (Day 0) and one on the day (Last Day) on which the TFR had been exceeded a threshold level (i.e., more than 10 times the TFR value observed on Day 0). During each OGTT, insulin pharmacokinetics (PK) and glucose pharmacodynamics (PD) were measured on delivery of a bolus of rapid-acting insulin. PK and PD responses were then regressed on the observed TFR values.

Results: Fourteen people with type 1 diabetes were invited to take part in the study. Of these, 2 withdrew consent due to personal reasons and 2 were excluded due to adverse events (skin irritation from adhesive tapes or accidental removal of infusion cannula). The 10 subjects who completed the study (2 women and 8 men) had a mean ±SD age of 31.1 ±7.7 years (range 21 - 44 years) and a mean ±SD body mass index of 26.7 ±2.8 kg/m^2 (range 23.5 - 30.9 kg/m^2). Their mean ±SD diabetes duration was 20.1 ±10.4 years (range 7 - 36 years), and their mean±SD HbA1c level was 61 ±6 mmol/mol (7.7 ±0.5 %; range 51 - 70 mmol/mol [6.8 - 8.6 %]). We observed that the mean±SE area under the plasma insulin curves ($AUC_{INSULIN}$) was substantially higher during the OGTTs on Day 0 than during the OGTTs performed after an average infusion site usage time of 10.4 days (Day 0: 23216 ±2939 pMol*min vs Last Day: 13543 ±2696 pMol*min; $p<0.01$). Additionally, the mean±SE plasma glucose concentration observed during the last two hours of the 5-h OGTT ($PG_{OGTTmean3\text{-}5hours}$) were significantly lower during the OGTT on Day 0 than during the OGTT performed after prolonged use of the infusion site (Day 0: 208.4 ±14.1 mg/dL vs Last Day: 302.4 ±17.4 mg/dL; $p<0.01$). Furthermore, the geometric mean */geometric standard deviation TFR level at the insulin infusion site progressively increased with usage duration (Day 0: 0.26 */4.16 kPa*s/µL vs Last Day: 37.17 */4.28 kPa*s/µL; $p<0.001$). Moreover, regression analysis of insulin, glucose, and TFR data showed that log-transformed TFR is strongly correlated with the $AUC_{INSULIN}$ ($r= -0.666$, $p<0.001$) and the $PG_{OGTTmean3\text{-}5hours}$ ($r= 0.815$, $p<0.001$).

Conclusions: Because of this strong relationship between TFR and indexes of insulin absorption efficiency, monitoring of TFR may allow the estimation of the prevailing insulin absorption efficiency and, in turn, may permit the determination of the optimal wear-time of an insulin infusion cannula.