Closing the loop, squaring the circle: Studies on insulin delivery, glucose monitoring and the artificial pancreas
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Chapter 5

Patch pump versus conventional pump: postprandial glycaemic excursions and the influence of wear time


On behalf of the AP@home consortium

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ABSTRACT

Background and aims: The aim of this study was to compare blood glucose and plasma insulin profiles after bolus insulin infusion by a patch pump versus a conventional pump, directly after placement and after day 3 of use.

Materials and methods: Twenty patients with type 1 diabetes came in for two blocks of visits: one block of two visits while wearing the OmniPod Insulin Pump (PP) and one block of two visits while wearing the Medtronic Paradigm Pump (CP). Patients administered an identical mealtime insulin bolus of at least 6 IU.

Results: For PP maximum glucose levels were 28.7% lower on day 3 (P=0.020), when maximum insulin levels were 30.3% higher (P=0.002). For CP maximum glucose levels were 26.5% lower on day 3 (P=0.015), when maximum insulin levels were 46.4% higher (P=0.003).

Mean glucose levels were significantly lower on day 3 for PP (168.2 (145.8) mg/dL vs. 139.4 (77.8), P=0.013), but not significantly so for CP (159.0 (66.1) mg/dL vs. 139.5 (57.9), P=0.084). Mean insulin levels were significantly higher on day 3 for CP (195 (120) pmol/L vs. 230 (90), P=0.01), but not significantly so for PP (178 (106) pmol/L vs. 194 (120), P=0.099). There were no significant differences between the two catheter lengths.

Conclusion: Postprandial glycaemic excursions were lower on day 3 of catheter wear time, but there were no differences between patch pumps and conventional pumps. These findings support that catheter wear time plays an important role in insulin absorption.
INTRODUCTION

Until recently all insulin pumps consisted of a needle inserted into the subcutaneous tissue, a housing (containing the insulin, electronics, pump and batteries) and a catheter connecting these two parts. Recently patch pumps were developed, to be carried directly on the skin, without the need to insert a needle manually and without a visible catheter (1-3). Internally these patch pumps still employ a catheter with a length of about 50 mm, substantially less than the 600 mm of catheter tubing used most often with catheter based pumps. It has been hypothesized that insulin catheters could influence insulin delivery (4). However, to our knowledge, there are no published studies investigating insulin absorption with these two types of insulin pumps with markedly different catheter lengths. For closed loop studies, in which insulin pumps are combined with subcutaneous glucose sensors to automatically compute and administer appropriate amounts of insulin to maintain euglycaemia, it is relevant to know if patch pumps (PP) and conventional insulin pumps (CP) induce different insulin absorption rates and to investigate reproducibility of insulin absorption. A reproducible and rapid absorption of the administered insulin is paramount to establish a successful Artificial Pancreas (AP). Additionally, recent evidence suggests that the duration the insulin catheter usage (wear time) influences the speed of insulin absorption from the subcutaneous tissue, in that the time to maximal insulin levels seems to decrease with a longer wear time (5,6). It is important to gain knowledge on the evolution of insulin pharmacokinetics with the progression of wear time of insulin pumps, since Model Predictive Control algorithms rely on adequate and accurate modelling of pharmacokinetic parameters. The aim of this study therefore, was to detect differences in postprandial glucose profiles and plasma insulin profiles after bolus insulin administration by a patch pump versus a conventional insulin pump while at the same time investigating the effect of catheter wear time on these profiles in patients with type 1 diabetes.
METHODS

Twenty patients participated in this multinational, randomized, cross-over, open-label trial (five in each of the four participating clinical centres of the AP@home consortium (Amsterdam – the Netherlands, Padova - Italy, Montpellier - France and Neuss - Germany)). Main inclusion criteria were a diagnosis of type 1 diabetes for at least 6 months, being treated with Continuous Subcutaneous Insulin Infusion (CSII) or Multiple Daily Insulin Injection (MDII) for at least 3 months, a body mass index (BMI) <35 kg/m² and an HbA1c level between 6 and 10%. Due to technical limitations concerning maximum insulin storage volume of the patch pump, and the fact that the pump had to be worn without intermittent change for 72 hours, only patients which a total daily insulin dose <66 U were included. Main exclusion criteria were pregnancy and use of medication known to impact glucose metabolism.

All patients completed an inclusion visit during which informed consent was obtained, after which patients were trained in use of the two pumps used in this trial. All patients were switched to insulin lispro (Eli Lilly and Company, Indianapolis, IN, USA). Patients were then randomized to undergo the main intervention in a cross-over design. The main intervention consisted of two blocks: one block of two visits while wearing the Omnipod Insulin Pump (Insulet Corp, Bedford, MA, USA) and one block of two visits while wearing a Medtronic Paradigm Veo Pump with the MMT-399 Quick-set Paradigm insulin infusion catheter set with a tubing length of 60 cm (Medtronic Diabetes, Northridge, CA, USA). The two visits within one block were 48 hours apart in order to determine the effect of catheter wear time (figure 1a). Prior to each block a new catheter/PP was placed in the abdominal region of the patients.

After the first visit in a block, patients were discharged and continued to wear the pump at home to return after 48 hours for a second visit with the same pump to allow for the assessment of the effect of wear time. Upon completion of a block the pump would be removed and patients returned to their usual insulin therapy. For the visits, patients reported to the Clinical Research Center (CRC) in a fasting state at 8 a.m. when blood sampling for glucose and plasma insulin determinations were started to record baseline values. If baseline blood glucose was >140 mg/dL, glycaemia was stabilized to euglycaemic levels (65-140 mg/dL) by intravenous administration of
insulin and the start of the study was delayed. Patients received breakfast at 9 a.m., of a composition which was customary to them, accompanied by their individually determined mealtime insulin bolus via the PP or CP (figure 1b). However, in all cases the meal bolus was at least 6 U to ensure sufficient increases in insulinemia during the visits. On all study days for a given patient, the same insulin dose was applied to cover an identical breakfast. Patients were also not allowed to change their basal insulin rates during the trial. Blood was sampled for plasma insulin and blood glucose determination until 4.5 hours postprandially (once every 10 minutes for the first 2 h and subsequently every 15 minutes for the next 2.5 h (figure 1B)). Blood glucose levels were determined at the bedside by a laboratory method (YSI 2300 STAT PLUS; YSI Incorporated, Yellow Springs, OH). Heparinized plasma was frozen and stored for later determination of insulin levels using an insulin chemiluminescence assay (Invitron Ltd, Monmouth, UK) at a central laboratory (The Institute of Life Sciences, Swansea University, UK).

Upon completion of the trial blood glucose and plasma insulin data were used to construct postprandial profiles. Time to peak, mean, maximum and Area under the Curve (AUC) of postprandial plasma insulin and blood glucose levels following administration of a mealtime insulin bolus with CP and PP were calculated. Maximum excursions for postprandial blood glucose levels were also assessed. Outcomes of these measures were compared between the two different types of pumps (interpump), as well as between the use of the same pump on visit 1 and visit 2 of each block (intrapump). Measures were compared using a paired t-test or the Wilcoxon signed rank test where appropriate. Statistical analysis was performed in PASW Statistics 18.0 (IBM Corp, Armonk, NY, USA) on an intention to treat basis.
Figure 1: A: Patients completed two blocks of 2 visits, totaling four study visits to the CRC. Two while wearing a conventional insulin pump (CP) and two while wearing a patch pump (PP). The two visits within one block, in which the same pumps were used, were 48 hours apart. Each visit took 5.5 hours to complete. B: Within each visit patients arrived at the CRC at 08.00. Blood samples for glucose and plasma insulin determination were collected every 15 min. The sampling rate was increased after the breakfast which was served to patients and continued until 4.5 hours postprandially.

RESULTS

Of the 20 included patients, one patient was unable to complete the second visit while wearing the patch pump.

Technical issues
There was technical failure of the Omnipod patch pump in 5 cases, in 1 case the Omnipod dislodged from the body of the participant. The catheter based pump had 1 technical failure. In all these cases the pumps were replaced and the entire block of two visits while wearing the affected pump was rescheduled.
**Baseline levels**

Baseline glucose concentrations needed to be stabilized in 23 out of 79 visits (6.1%, 13 visits with PP and 7.9%, 10 visits with CP). Baseline glucose was 117.1 (25.7) mg/dL on day 1 of using the patch pump (PP) vs. 110.4 (27.3) on day 3 of use, for the catheter based pump (CP) this was 119.5 (20.2) vs. 109.8 (27.6) mg/dL, without significant difference between glucose baseline levels (overall $P=0.392$). Baseline insulin for PP was 103.6 (106.1) pmol/L on day 1 of use vs. 123.1 (163.5) on day 3. For CP this was 118.9 (115.8) vs. 138.1 (129.5) pmol/L, without significant difference between insulin baseline levels (overall $P=0.392$).

**Glucose levels**

Mean postprandial glucose curves are displayed in figure 2. Maximum postprandial glucose levels were significantly lower in both the patch pump (PP) and catheter based pump (CP) on the third day of use. For PP, the maximum glucose level was 223.0 (101.6) mg/dL (median (IQR)) on day one of use versus 159.0 (97.2) on day 3 ($P=0.02$). For CP, the maximum glucose level was 223.0 (83.0) mg/dL (median (IQR)) on day one of use versus 164.0 (74.8) on day 3 ($P=0.015$). Time to this maximum postprandial glucose value (time-to-peak) was not significantly different between day one and three of use for both PP (120 (90) min vs. 110 (140), $P=0.226$) and CP (110 (85) min vs. 150 (145), $P=0.556$). The maximum glucose excursion (difference between lowest and highest postprandial glucose levels) was significantly lower on day 3 of use for both PP (134.0 (66.4) mg/dL on day 1 vs. 83.0 (59.5), $P=0.012$) and CP (120.0 (68.0) mg/dL vs. 89.3 (50.9), $P=0.002$). Mean glucose levels were significantly lower on day 3 for PP (168.2 (145.8) mg/dL vs. 139.4 (77.8), $P=0.013$), but not significantly so for CP (159.0 (66.1) mg/dL vs. 139.5 (57.9), $P=0.084$).

Area under the curve was significantly lower on day 3 of use for PP (46579.0 (25691.0) mg/dL*min, vs. 37893.0 (21812.0), $P=0.013$) but not significantly so for CP (44431.0 (19439.0) mg/dL*min vs. 36358.0 (16547.0), $P=0.084$). For all glucose outcome measures there were no significant interpump differences (day 1 CP vs. day 1 PP and day 3 CP vs. day 3 PP) (data not shown).
\textit{Plasma Insulin levels}

Mean postprandial insulin profiles are displayed in figure 3. Maximum postprandial insulin levels were significantly higher in both the patch pump (PP) and catheter based pump (CP) on the third day of use. For PP, the maximum insulin level was 274.0 (305.0) pmol/L (median (IQR)) on day one of use versus 357.0 (225.0) on day 3 \((P=0.002)\). For CP, the maximum insulin level was 295.0 (206.0) pmol/L (median (IQR)) on day one of use versus 432.0 (207.0) on day 3 \((P=0.003)\). Time to this maximum postprandial insulin value (time-to-peak) was significantly shorter on day 3 for PP \((60.0 (50.0) \text{ min vs. } 40.0 (20.0), P=0.017)\), but not significantly so for CP \((60.0 (70.0) \text{ min vs. } 50.0 (50.0), P=0.218)\).

Mean insulin levels were significantly different on day 3 for CP \((195 (120) \text{ pmol/L vs. } 230 (90), P=0.010)\), but not significantly so for PP \((178 (106) \text{ pmol/L vs. } 194 (120), P=0.099)\).

Area under the curve was not different on day 3 of use for both PP \((50968.0 (31190.0) \text{ pmol/L*min, vs. } (51240.0 (34572.0), P=0.601)\) and CP \((51563.0 (23048.0) \text{ pmol/L*min vs. } 59043.0 (2435.0), P=0.351)\). For all insulin outcome measures there were no significant differences interpump (day 1 CP vs. day 1 PP and day 3 CP vs. day 3 PP) \(\text{(data not shown)}\).

\textbf{Figure 2:} Mean postprandial glucose excursions for day 1 and 3 of patch pump (PP) use and catheter-pump (CP) use.
DISCUSSION

In this study we showed that insulin absorption is significantly faster on day 3 of use of an insulin pump, resulting in lower postprandial glucose values. These findings suggest that the wear time of the insulin catheter determines insulin absorption. The absence of any difference between PP and CP suggests that the influence of tubing length, if any, is negligible.

These findings are corroborated by studies investigating the trauma induced by insertion of the catheter tip by a needle into the subcutaneous fat. After insertion marked increases in adipose tissue blood flow have been demonstrated up to two days after insertion, combined with faster absorption of insulin up to four days after insertion (5). This is in line both with the observed timeframes in this study and with our finding that pharmacokinetic parameters as time-to-peak and maximum insulin levels changed, but AUC did not. In other words, there was no difference in total absorbed insulin. Insulin was absorbed more swiftly if the infusion site was 3 days old. The current advice to change insulin catheters after 3 days is supported by literature (7), however patients often use their catheters longer and further research is needed to determine the effects of this increased wear time.

Figure 3: Mean postprandial insulin profiles for day 1 and 3 of patch pump (PP) use and catheter-pump (CP) use.
The change in insulin pharmacokinetics over the course of the wear time of insulin pumps, and more specifically over the course of the ageing insertion site, could influence closed loop therapy. Indeed, we conducted this trial with the primary aim to the gain knowledge to improve closed loop model predictive control algorithms. Control algorithms could be made aware of a catheter change and could thus anticipate upon changes in insulin pharmacokinetics, thereby possibly improving glycaemic control during closed loop. The same is true for automated bolus calculators, which could use this information to suggest a more appropriate bolus amount. In addition, the field of closed loop control is investigating a “single-port” approach (8,9), in which the glucose sensor necessary for closed loop control is physically coupled to the insulin infusion catheter and reside within the same infusion site. With glucose sensors having a lifetime ranging from 5 to 7 days, which therefore could in principle extend the time the catheter-sensor combination remains in situ for this amount of time, insulin pharmacokinetics could change even more over time than we were able to measure in this study.

This study has demonstrated that as time progresses from the moment of catheter placement, insulin is absorbed more quickly from the infusion site. This study has also shown that these changes in insulin pharmacokinetics are clinically relevant, resulting in less pronounced postprandial glucose curves with older catheters. Patients and physicians should be aware of the temporarily diminished insulin absorption which occurs when changing insulin infusion sites. This knowledge could also help to improve upon closed loop control algorithms which could more accurately predict the effects of insulin infusion, bringing us a small step closer to a safe and effective artificial pancreas.
REFERENCE LIST