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ORIGINAL ARTICLE

Patch Pump Versus Conventional Pump: Postprandial Glycemic Excursions and the Influence of Wear Time

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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 (PP) versus a conventional pump (CP), directly after placement and after Day 3 of use.
Patients and Methods: Twenty patients with type 1 diabetes came in for two blocks of visits: one block of two visits while wearing the OmniPod® (Insulet Corp., Bedford, MA) insulin pump (PP) and one block of two visits while wearing the Medtronic Diabetes (Northridge, CA) 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 ($P=0.003$). Glucose levels (mean [interquartile range]) were significantly lower on Day 3 for PP (168.2 [145.8] mg/dL vs. 139.4 [77.8] mg/dL; $P=0.013$), but not significantly so for CP (159.0 [66.1] mg/dL vs. 139.5 [57.9] mg/dL; $P=0.084$). Mean insulin levels were significantly higher on Day 3 for CP (195 [120] pmol/L vs. 230 [90] pmol/L; $P=0.01$), but not significantly so for PP (178 [106] pmol/L vs. 194 [120] pmol/L; $P=0.099$). There were no significant differences between the two catheter lengths.
Conclusions: Postprandial glycemic excursions were lower on Day 3 of catheter wear time, but there were no differences between PPs and CPs. These findings support the proposal 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 (PPs) were developed, to be worn directly on the skin, without a visible catheter.[1–3] Internally these patch pumps still use a catheter with a length of about 5 cm, substantially less than the 60 cm of catheter tubing used most often with catheter-based pumps.

It has been hypothesized that insulin catheters and the duration of insulin catheter usage 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 euglycemia, it is relevant to know if PPs and conventional pumps (CPs) for insulin 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. Additionally, recent evidence suggests that wear time influences the speed of insulin absorption from the subcutaneous

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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 because model predictive control algorithms rely on adequate and accurate modeling 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 PP versus a CP for insulin while at the same time investigating the effect of catheter wear time on these profiles in patients with type 1 diabetes.

Patients and Methods

Twenty patients participated in this multinational, randomized, crossover, open-label trial (five in each of the four participating clinical centers 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 or multiple daily insulin injection for at least 3 months, a body mass index of <35 kg/m^2, and a hemoglobin A1c level between 6% and 10%. Because of technical limitations concerning maximum insulin storage volume of the PP and the fact that the pump had to be worn without intermittent change for 72 h, only patients with a total daily insulin dose of <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 the use of the two pumps used in this trial. All patients were switched to insulin lispro (Eli Lilly and Co., Indianapolis, IN). Patients were then randomized to undergo the main intervention in a crossover design. The main intervention consisted of two blocks: one block of two visits while wearing the OmniPod® insulin pump (Insulet Corp., Bedford, MA), which was remotely controlled by the First Generation Personal Diabetes Manager (Insulet Corp.), and one block of two visits while wearing a Medtronic Diabetes (Northridge, CA) Paradigm® Veo™ pump with the MMT-399 Quick-set Paradigm insulin infusion catheter set with a tubing length of 60 cm (Medtronic Diabetes). The two visits within one block were 48 h apart in order to determine the effect of catheter wear time (Fig. 1A). Directly at the beginning of each block a new catheter/PP was placed in the abdominal region of the patients, with the catheter-based pump was carried on the waist. After the first visit in a block, patients were discharged and continued to wear the pump at home to return after 48 h 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 in a fasting state at 8 a.m., when blood sampling for glucose and plasma insulin determinations were started to record baseline values. If the baseline blood glucose level was >140 mg/dL, glycemia was stabilized to euglycemic 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 that was customary for them, accompanied by their individually determined mealtime insulin bolus via the PP or CP (Fig. 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 h postprandially (once every 10 min for the first 2 h and subsequently every 15 min for the next 2.5 h) (Fig. 1B). Blood glucose levels were determined at the bedside by a laboratory method (YSI 2300 STAT PLUS glucose and lactate analyzer; YSI Inc., Yellow Springs, OH). Heparinized plasma was frozen and stored for later determination of insulin levels using an insulin chemiluminescence assay (Invitron Ltd., Monmouth, United Kingdom) at a central laboratory (The Institute of Life Sciences, Swansea University, Swansea, Wales, United Kingdom).

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 of postprandial plasma insulin and blood glucose levels following administration of a mealtime insulin bolus with CP and PP were calculated using the trapezoid rule. 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 version 18.0 (IBM Corp., Armonk, NY) on an intention-to-treat basis.

Results

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

Technical issues

There was technical failure of the OmniPod PP in five cases, and in one case the OmniPod dislodged from the body of the participant. The catheter-based pump had one 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 (13 out of 39 visits with PP and 10 out of 40 visits with CP; $P = 0.607$). Stabilization of baseline was equally distributed among Day 1 (11 times) and Day 3 (12 times) of use ($P = 0.998$). Mean (SD) baseline glucose was 117.1 (25.7) mg/dL on Day 1 of using PP versus 110.4 (27.3) mg/dL on Day 3 of use, whereas for CP this was, respectively, 119.5 (20.2) mg/dL versus 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 versus 123.1 (163.5) pmol/L on Day 3; for CP, respectively values were 118.9 (115.8) and 138.1 (129.5) pmol/L, without significant difference between insulin baseline levels (overall $P = 0.392$).

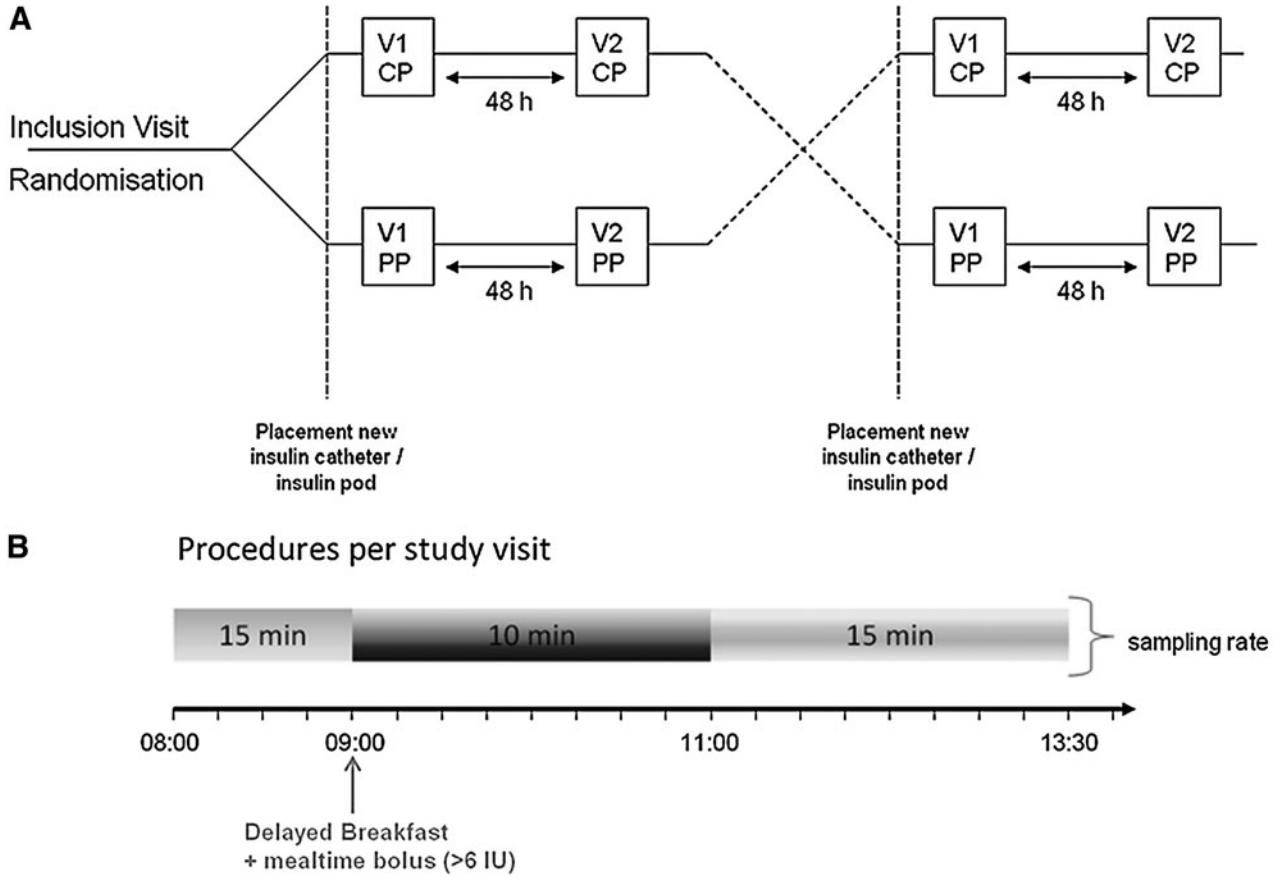

FIG. 1. **(A)** Patients completed two blocks of two visits, totaling four study visits to the clinical research center: two while wearing a conventional pump (CP) for insulin and two while wearing a patch pump (PP). The two visits (V1 and V2) within one block, in which the same pumps were used, were 48 h apart. Each visit took 5.5 h to complete. **(B)** Within each visit patients arrived at the clinical research center at 8:00 a.m. Blood samples for glucose and plasma insulin determination were collected every 15 min. The sampling rate was increased after the breakfast that was served to patients and continued until 4.5 h postprandially.

Glucose levels

Mean postprandial glucose curves are displayed in Figure 2. Maximum postprandial glucose levels were significantly lower in both PP and CP on Day 3 of use. For PP, the median (interquartile range) maximum glucose level was 223.0 (101.6) mg/dL on Day 1 of use versus 159.0 (97.2) mg/dL on Day 3 ($P=0.02$). For CP, the corresponding maximum glucose level was 223.0 (83.0) mg/dL on Day 1 of use versus 164.0 (74.8) mg/dL on Day 3 ($P=0.015$). Time to this maximum postprandial glucose value (time-to-peak) was not significantly different between Day 1 and Day 3 of use for both PP (120 [90] min vs. 110 [140] min; $P=0.226$) and CP (110 [85] min vs. 150 [145] min; $P=0.556$). 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] mg/dL; $P=0.012$) and CP (120.0 [68.0] mg/dL vs. 89.3 [50.9] mg/dL; $P=0.002$).

Mean (SD) glucose levels were significantly lower on Day 3 for PP (168.2 [145.8] mg/dL vs. 139.4 [77.8] mg/dL; $P=0.013$), but not significantly so for CP (159.0 [66.1] mg/dL vs. 139.5 [57.9] mg/dL; $P=0.084$).

Area under the curve was significantly lower on Day 3 of use for PP (46,579.0 [25,691.0] mg/dL·min vs. 37,893.0 [21,812.0] mg/dL·min; $P=0.013$) but not significantly so for CP (44,431.0 [19,439.0] mg/dL·min vs. 36,358.0 [16,547.0] mg/dL·min; $P=0.084$). 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).

Plasma insulin levels

Mean postprandial insulin profiles are displayed in Figure 3. Maximum postprandial insulin levels were significantly higher with both PP and CP on Day 3 of use. For PP, the median [interquartile range) maximum insulin level was 274.0 (305.0) pmol/L on Day 1 of use versus 357.0 (225.0) pmol/L on Day 3 ($P=0.002$). For CP, the maximum insulin level was 295.0 (206.0) pmol/L on Day 1 of use versus 432.0 (207.0) pmol/L 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] min vs. 40.0 [20.0] min; $P=0.017$) but not significantly so for CP (60.0 [70.0] min vs. 50.0 [50.0] min; $P=0.218$).

Mean (SD) insulin levels were significantly different on Day 3 for CP (195 [120] pmol/L vs. 230 [90] pmol/L; $P=0.010$) but not significantly so for PP (178 [106] pmol/L vs. 194 [120] pmol/L; $P=0.099$).

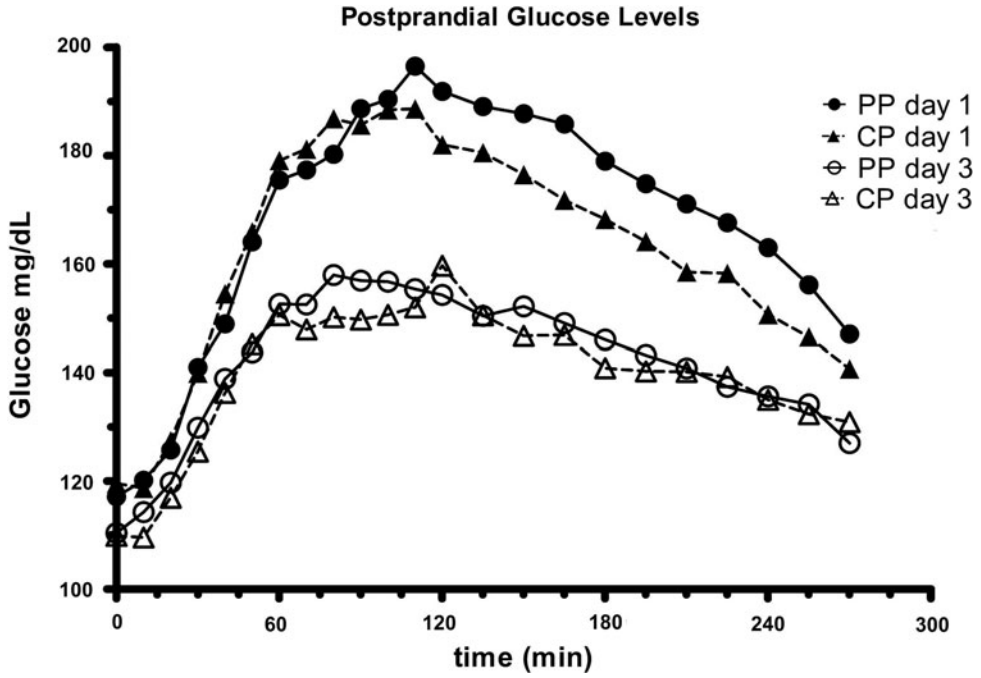

FIG. 2. Mean postprandial glucose excursions for Day 1 and Day 3 of patch pump (PP) and catheter-based conventional pump (CP) use.

Area under the curve was not different on Day 3 of use for either PP (50,968.0 [31,190.0] pmol/L·min vs. 51,240.0 (34,572.0) pmol/L·min; $P = 0.601$) or CP (51,563.0 [23,048.0] pmol/L·min vs. 59,043.0 [2435.0] pmol/L·min; $P = 0.351$). 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) (data not shown).

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

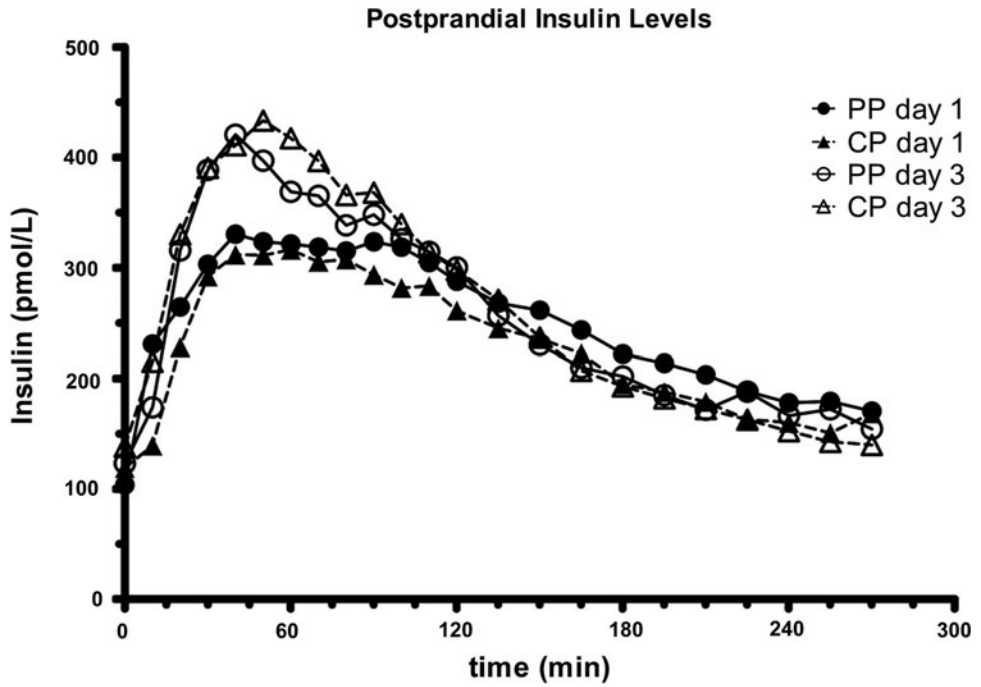

FIG. 3. Mean postprandial insulin profiles for Day 1 and Day 3 of patch pump (PP) and catheter-based conventional pump (CP) use.

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 2 days after insertion, combined with faster absorption of insulin up to 4 days after insertion.[5] This is in line both with the observed time frames in this study and with our finding that pharmacokinetic parameters as time-to-peak and maximum insulin levels changed, but area under the curve 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 the literature[7]; however, patients often use their catheters longer, and further research is needed to determine the effects of this increased wear time.

The change in insulin pharmacokinetics over the course of the wear time of insulin pumps, and more specifically over the course of the aging insertion site, could influence closed-loop therapy. Control algorithms could be made aware of a catheter change and could thus anticipate upon changes in insulin pharmacokinetics, thereby possibly improving glycemic control during closed loop. The same is true for automated bolus calculators, which could use this information to suggest a more appropriate bolus amount. Alternatively, simultaneous injection of hyalonuridase could be used, as this has been shown to improve the consistency of subcutaneous insulin absorption.[8] In addition, the field of closed-loop control is investigating a "single-port" approach,[9,10] in which the glucose sensor necessary for closed-loop control is physically coupled to the insulin infusion catheter and resides 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 that occurs when changing insulin infusion sites. This knowledge could also help to improve upon closed-loop control algorithms that could more accurately predict the effects of insulin infusion, bringing us a small step closer to a safe and effective artificial pancreas.

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Author Disclosure Statement

J.H.DeV. reports having received grants and speaker fees from Medtronic. Y.M.L., S.A., C.B., A.F., J.P., R.S., A.A., D.B., E.R., and L.H. have no competing financial interests. Y.M.L. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Y.M.L. wrote the manuscript and protocol, performed analysis, and gathered data. S.A., C.B., A.F., J.P., and R.S. gathered data. A.A. and D.B. gathered data and reviewed the manuscript. E.R., L.H., and J.H.DeV. reviewed the protocol and the manuscript.

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