In Vivo Flow Evaluation and Correlation to Insulin Pharmacokinetics of Continuous Subcutaneous Insulin Infusion Sets

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Background

Continuous subcutaneous insulin infusion (CSII) sets have been called the "Achilles heel" of infusion pump therapy, with known failure modes including leakage, occlusion alarms[1-3], and "silent" occlusions[4-5]. Silent occlusions are characterized by in-line infusion pressure excursions that may indicate flow interruptions below insulin pump alarm thresholds.[4-5] Inconsistent flow may lead to irregular blood glucose and increase the potential for hyperglycemia in some patients. Unexplained hyperglycemia is a common occurrence in T1D on pump therapy.[6]

A novel infusion set (BD FlowSmart™) is in development to stabilize flow. To assess flow performance, in-line infusion pressure was recorded during insulin lispro infusion in a swine model, and flow interruptions were quantified by a novel pressure/flow algorithm. Insulin pharmacokinetics (PK) were measured to correlate in vivo flow performance with physiological insulin uptake to establish predictive models of insulin delivery and flow fault detection.

Methods

Study Design & Data Collection:

- Insulin was delivered via commercial insulin pump over a series of infusion profiles using 2 commercial CSII sets (1 steel, 1 polymer catheter) and 1 investigational (polymer catheter) set.
- In-line infusion pressure and insulin PK were simultaneously monitored at clinically relevant infusion rates (1U/hr basal; 4U/bolus) per Table 1.
- N=11 nondiabetic Yorkshire swine during insulin lispro delivery. Each study arm was run in 1-2 replicates in every animal per Table 1.

Arm	Device	Study Description	Replicates
1	Accu-chek® Rapid-D 28G steel cannula, 6 mm length	4U lispro bolus.	1 per swine (11 total)
2	Accu-chek® Rapid-D 28G steel cannula, 6 mm length	1U/hr lispro basal for 4 hrs with forced occlusion at hours 2 -3.*	1 (11)
3	Accu-chek® Rapid-D 28G steel cannula, 6 mm length	1U/hr lispro basal for 4 hrs.*	1 (11)
4	BD FlowSmart™ (Investigational set) 28G polymer catheter, 6 mm length	1U/hr lispro basal for 4 hrs.*	2 (22)
5	Medtronic Quick-set® 25G polymer catheter, 6 mm length	1U/hr lispro basal for 4 hrs.*	2 (22)

Table 1. Arms of devices & insulin delivery profiles. *Hrs 4-5: 1U/hr with forced occlusion.

- Insulin levels were analyzed via a lispro-specific radioimmunoassay (Millipore, Billerica, MA,) with validated LLOQ of 1.953 µU/ml. Serum samples were collected from standardized, timed blood draws.
- In-line infusion pressure was monitored with a commercial pressure transducer then analyzed with a proprietary pressure/flow algorithm to identify periods of flow interruption indicated by rising in-line infusion pressure.[7] Flow interruption frequency & duration were calculated, as well as percent time total flow was interrupted relative to infusion profile.

Insulin PK Modeling:

- Model parameter estimation was performed on Arms 1 & 3 using minimization of the weighted prediction errors with Nelder-Mead algorithm (total error = 0.5 error arm 1 + 0.5 error arm 3).
- Dose response profiles were modeled 2 ways: (1) based on theoretical, optimized input of 1U/hr, and (2) using intermittent dose input function as derived from the flow interruption detection algorithm.
- The flow interruption detection algorithm was configured with no minimum duration of interruption. Precision of model prediction was assessed via root mean square error (RMSE) with experimental PK (measured lispro values).

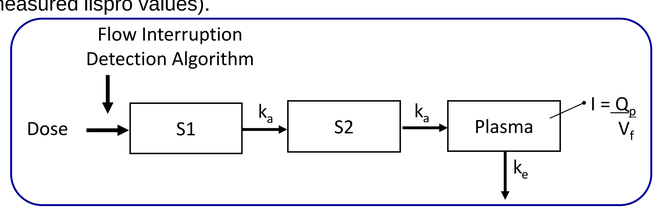
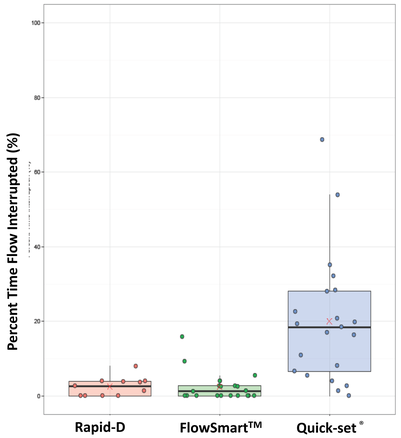


Figure 1. Two compartment PK model used to fit measured insulin data.[8]

Results

- When comparing polymer catheter sets, BD FlowSmart™ showed reduction in flow interruption frequency, duration, & 88% reduction in percent time total flow was interrupted compared to Quick-set® (p<0.001), Figure 2.
- There were no statistically significant differences in pump occlusion alarm or leakage occurrences among device types.



Infusion Set	Rapid-D	Quick-Set®	Flow Smart™
n	11	21	21
# Flow interruptions	9	76	20
Mean interruption duration (min)	6	49	6
Mean % time total flow interrupted	2.51	20	2.46
Reduction in mean % time flow interrupted		88%	
One sided Wilcoxon test		p < 0.001	

Figure 2. (A) Boxplot of mean percent time flow interrupted per device type. X represents mean value. (B) Results summary table.

- Predicted PK concentration time profiles modeled based on theoretical input function of 1U/hr did not capture PK irregularities caused by unalarmed, intentional occlusions in devices used as a positive control (Arm 2) when flow interruptions were not incorporated. See Fig. 3, columns with no pressure input.
- PK prediction model fit for intentionally occluded devices (Arm 2) was improved by incorporating flow interruptions derived from the pressure/flow algorithm into input functions ($p < 0.05$ per non-parametric testing of RMSE). See Fig. 3, columns with pressure input for improved fit of PK prediction model (blue line) to measured lispro values (black dotted line with pink smoothing spline).

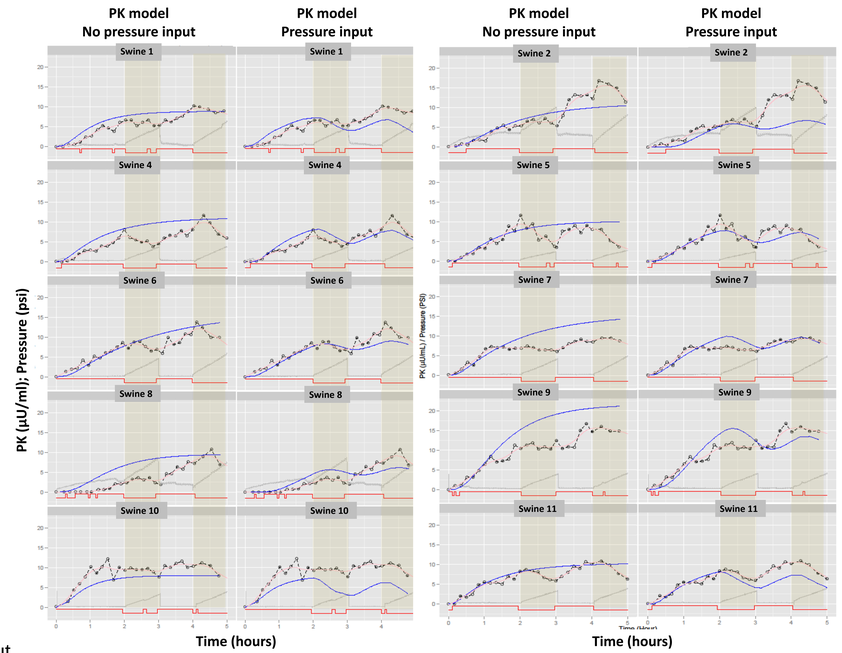


Figure 3. PK models with and without pressure input displayed for intentionally occluded profiles (Arm 2) at hours 2-3 & 4-5, shown as yellow bars. PK prediction model (blue line) shows improvement in fit to measured lispro values (black dotted line with pink smoothing spline) when pressure is incorporated into model (right plot per swine). Infusion pressure values (gray line, unit: psi) shown with algorithm identified flow interruptions (red line, 0=flow, -1=no flow).

- Measured lispro
- Smoothed lispro measurements
- Predicted PK
- Flow interruptions detected by algorithm
- Pressure (psi)

Conclusions

- The consistency & reliability of subcutaneous insulin infusion is affected by multiple parameters including sub-optimal CSII set delivery with intermittent undiagnosed silent occlusions. Stabilizing infusion pressure and reducing flow faults may enable more predictable and consistent insulin delivery.
- Infusion pressure may be a good indicator of insulin flow reliability and can provide high sensitivity occlusion detection below pump alarm thresholds. These sub-alarm events can be detected and quantified when analyzed by the proprietary pressure/flow algorithm.
- The investigational set (BD FlowSmart™) showed improved insulin flow reliability relative to the commercial polymer set (Quick-set®) based on detectable silent occlusion reduction as identified by the pressure/flow algorithm.
- The use of infusion pressure input parameters into the theoretical PK prediction model improves fit to measured lispro values when flow interruption periods were ~1 hour, but lacked the sensitivity to improve fit for smaller flow interruption durations.
- Additional optimization to improve sensitivity for shorter duration and more irregular flow interruptions is required. Compensation for other factors affecting PK variability (e.g. insulin absorption, assay variability, tissue site effects, animal growth variation) may improve model fitting differences. In addition, other methods such as population modeling or PK simulations using Artificial Pancreas simulators may enable better assessment of flow variability impact on PK.

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