DIABETES TECHNOLOGY & THERAPEUTICS
Volume 13, Number 4, 2011

DOI: 10.1089/dia.2010.0183

# Microneedle-Based Intradermal Versus Subcutaneous Administration of Regular Human Insulin or Insulin Lispro: Pharmacokinetics and Postprandial Glycemic Excursions in Patients with Type 1 Diabetes

Ronald J. Pettis, Ph.D.,[1] Laurence Hirsch, M.D.,[2] Christoph Kapitza, M.D.,[3] Leszek Nosek, M.D.,[3] Ulrike Hövelmann, M.D.,[3] Heinz-Joerg Kurth, M.D., Ph.D.,[3] Diane E. Sutter,[1] Noel G. Harvey, Ph.D.,[1] and Lutz Heinemann, Ph.D.[3]

## Abstract

***Background:*** This study assessed pharmacokinetics (PK) and pharmacodynamic postprandial glycemia (PPG) in patients with type 1 diabetes mellitus (T1DM) after a standardized liquid meal following insulin lispro (IL) or regular human insulin (RHI) given by microneedle-based intradermal (ID) versus subcutaneous (SC) delivery.
***Research Design and Methods:*** In this randomized, open-label, five-way crossover study, 29 T1DM patients received IL and RHI (0.125 U/kg) at 2 min and 17 min premeal, respectively, by both the SC and ID routes and also received RHI by the ID route at 2 min premeal. Blood glucose was stabilized at 120 mg/dL prior to a standardized 82-g carbohydrate liquid meal. ID delivery used a 34-gauge 1.5-mm steel microneedle, and SC delivery used a 31-gauge 8-mm syringe needle.
***Results:*** The 90-min PPG (blood glucose area under the curve for 0–1.5 h) for ID RHI was 14% lower than SC RHI at −17 min ($P < 0.0001$) and 11% lower than ID RHI at −2 min ($P = 0.0006$). PPG did not differ between ID RHI and SC IL, both at −2 min ($P = 0.8345$). ID IL PPG was lower than SC, both at −2 min, but not significantly ($P = 0.10$). Both ID IL and ID RHI PK data showed significantly faster uptake and time to maximum concentration, higher maximum concentration, and shorter systemic circulating duration versus SC dosing. ID IL and RHI delivery was generally well tolerated.
***Conclusions:*** PPG with RHI administered ID via microneedle was improved versus SC delivery when dosed 17 min premeal. ID RHI provided similar control of PPG as SC IL immediately premeal. Further studies of ID insulin delivery via steel microneedles are warranted.

## Introduction

The treatment paradigm for diabetes, which traditionally emphasized reducing fasting blood glucose (BG) and glycosylated hemoglobin (HbA1c), has broadened in the past decade to also encompass optimizing control of postprandial hyperglycemia.[1] This shift has occurred in response to demonstrations that postprandial hyperglycemia contributes significantly to high HbA1c concentrations and may be an independent risk factor for cardiovascular complications.[2–8] Postprandial hyperglycemia develops early in the course of type 2 diabetes[9] and can occur very frequently even in the context of apparently good metabolic control.[10]

Among type 1 (T1DM) or type 2 diabetes mellitus patients on insulin therapy, the magnitude of postprandial glucose (PPG) excursion depends on several factors, including insulin dosage, the injection–meal interval, and the insulin absorption rate.[11] Rapid-acting insulin analogs such as insulin lispro (IL) exhibit faster absorption than regular human insulin (RHI) after peripheral subcutaneous (SC) administration but still fall short of native physiologic insulin secretion by the pancreas, which can peak within minutes of nutrient ingestion. Postprandial hyperglycemia and delayed hypoglycemia remain significant problems.[12,13]

Recently microneedle syringe devices (Soluvia™, Becton Dickinson, Franklin Lakes, NJ) have been approved for

[1]BD Technologies, Research Triangle Park, North Carolina.
[2]BD Medical–Diabetes Care, Franklin Lakes, New Jersey.
[3]Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany.
This study has the number 2007-003924-39 with EudraCT at eudract.emea.europa.eu and NCT00553488 at ClinicalTrials.gov.

intradermal (ID) delivery of flu vaccine. Similar but even finer-gauge investigational systems (34-gauge, 1.5-mm microneedle catheters) are under investigation for insulin delivery and their potential to improve PPG control. These stainless steel microcannulae penetrate the stratum corneum and epidermis to reach the microcapillaries and lymphatic vessels of the dermis.[14] In both preclinical swine pharmacokinetics (PK) studies[15] and a clinical study of ID IL under euglycemic glucose clamp conditions in 10 healthy volunteers,[16] delivery via microneedles 1.25–1.75 mm long produced faster insulin uptake than SC delivery. PK outcomes included higher maximum insulin concentration ($C_{max}$) and shorter time to $C_{max}$ ($t_{max}$). Additionally, in the clinical study, ID IL administration yielded more physiologic pharmacodynamics (PD) including both a more rapid effect of insulin (shorter time to maximal glucose infusion rate [GIR]) and a faster offset of insulin action (shorter time to late half-maximal GIR).[16] The study reported herein was conducted to determine whether the more rapid absorption of ID insulin resulting from microneedle administration translates into a significant reduction in PPG in patients with T1DM under standardized meal conditions.

## Subjects and Methods

### *Study factors and objectives*

Factors under investigation (Table 1) included delivery route (ID vs. SC), insulin type (RHI vs. IL), and dosing time relative to the meal (−17 vs. −2 min premeal). The following study hypotheses were evaluated: (1) ID insulin PPG control is better versus SC for either insulin when administered at equivalent times; (2) ID administration renders RHI PPG similar to SC IL when administered at equivalent times; (3) ID administration affords similar PPG between RHI and IL, making both insulin types equally effective when given at equivalent times; and (4) PPG for ID RHI administration is better with earlier versus later administration before a meal (Table 1).

### *Patients*

Eligible patients were men 18–55 years old on intensified insulin therapy for T1DM (duration of diabetes ≥1 to <15 years, HbA1c ≤9.0%). Exclusion criteria included gastroparesis, impaired hepatic or renal function, uncontrolled hypertension (systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg), recurrent major hypoglycemia or hypoglycemic unawareness as judged by the investigator, or use of any medication known to interfere with glucose metabolism unless that medication was initiated at least 3 months before screening.

### *Procedures*

The protocol for this single-site, randomized, open-label, five-period crossover study (NCT00553488 at ClinicalTrials.gov) was developed jointly by the sponsor and the investigators. It was approved by an institutional review board, and the study was conducted in accordance with the principles stated in the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practices. All patients provided written, informed consent.

The study comprised a screening visit and 5 treatment days separated by 3–21-day washout periods. Patients were required to fast for at least 8 h and to discontinue short-acting insulin for 6 h and long-acting insulin for 12 h (NPH) or 24 h (insulin glargine, insulin detemir) before each study day. Patients using insulin pumps were required to suspend their basal infusion 2 h before arrival at the clinic and to disconnect the pump upon arrival. At the study start, patients were connected to a Biostator (mtb Medizintechnik, Ulm, Germany), and BG was adjusted to 120 mg/dL with a variable intravenous delivery of glucose and/or insulin aspart (NovoRapid®, Novo Nordisk, Bagsvaerd, Denmark). On the first treatment day at $t = -60$ min premeal, the insulin aspart intravenous infusion rate was locked at a level where BG remained stable without concomitant glucose infusion. This patient-specific intravenous insulin aspart infusion rate was applied for the remainder of the study period and on subsequent treatment days to compensate for basal insulin metabolic activity that would normally have been present in addition to the prandial insulin dosage under investigation.

Table 1. Clinical Study Arms for the Five-Period Randomized Crossover Comparing Preprandial Intradermal and Subcutaneous Delivery of Insulin Lispro and Regular Human Insulin

| *Insulin type* | *Administration route* | *Premeal injection time* |
|---|---|---|
| IL | ID | −2 min |
| IL | SC | −2 min |
| RHI | ID | −2 min |
| RHI | SC | −17 min |
| RHI | ID | −17 min |

ID, intradermal; IL, insulin lispro; RHI, regular human insulin; SC, subcutaneous.

At $t = 0$ min, patients consumed, within a 3-min period, a standardized liquid meal of Resource energy drink (Novartis Nutrition GmbH, Munich, Germany), 400 mL containing 82 g of carbohydrates. IL (Humalog®, Eli Lilly, Indianapolis, IN) or RHI (Humulin®, Eli Lilly) at 0.125 U/kg was administered 17 min ($t = -17$ min) or 2 min ($t = -2$ min) before consumption of the liquid meal. Patients received, in a randomized sequence and at separate treatment visits, the following insulin administrations: SC IL, ID IL, and ID RHI at −2 min and SC RHI and ID RHI at −17 min. The SC IL at −2 min and SC RHI at −17 min served as control conditions. These regimens are both commonly practiced for insulin therapy. The time factors were chosen to reflect customary dosing habits of diabetes patients: immediate premeal dose of analog insulin and the recommended earlier premeal dosing for regular insulin. The carbohydrate load and the insulin dose were designed to allow relatively large PPG excursions under these control conditions.

Insulin was administered into the periumbilical abdominal wall. For ID dosing, insulin was infused over a short time period (500 μL or 50 U/min [0.83 U/s]) with a programmable syringe pump (Harvard PhD 2000, Harvard Apparatus, Holliston, MA) and a 1.5-mm, 34-gauge microneedle research catheter set (RCS, Becton Dickinson). The SC injections were done with an insulin syringe (BD Ultra Fine® II, 8-mm, 31-gauge needle, Becton Dickinson).

PPG was continuously monitored through 240 min after the meal. In addition, serial blood samples for determination of serum insulin and BG laboratory analysis (Super-GL

Ambulance glucose analyzer, Ruhrtal Labortechnik, Delecke-Möhnesee, Germany) were taken at prespecified intervals from 45 min premeal through 240 min postmeal. To differentiate administered IL or RHI formulations from the intravenous basal insulin aspart, specific non–cross-reactive immunoassays (IL radioimmunoassay [LPI-16K], Linco Research, St. Charles, MO; RHI chemiluminescent immunoassay [LIASON® CLIA], DiaSorin, Saluggia, Italy) were performed at a central laboratory (IKFE, Mainz, Germay).

After completion of study procedures on each treatment day, patients completed a survey in which they rated the perceived relative discomfort of the ID or SC insulin administration on a standard 15-cm pain visual analog scale (VAS). In addition, the study physician checked the site of insulin administration upon removal of the infusion device as well as 1 and 4 h later and scored any local reaction for erythema and edema according to the Draize scale.[17] Patients ate a regular meal before clinical discharge and were instructed to re-establish their usual insulin therapy.

### *Endpoints and statistics*

**PD.** The primary endpoint was the area under the curve (AUC) for the BG concentration–time profile during the 90 min after the meal (BG $AUC_{0–1.5\,h}$). Other PD endpoints were determined at predefined times or time intervals through 4 h postmeal and included the AUCs of the BG concentration–time profiles (BG $AUC_{0–0.5\,h}$ through BG $AUC_{0–4\,h}$), the maximum and minimum BG concentrations ($BG_{max,0–1.5\,h}$ through $BG_{max,0–4\,h}$ and $BG_{min,0–1.5\,h}$ through $BG_{min,0–4\,h}$, respectively) and corresponding differences, the times to maximum and minimum BG concentrations ($tBG_{max,0–1.5\,h}$ through $tBG_{max,0–4\,h}$ and $tBG_{min,0–1.5\,h}$ through $tBG_{min,0–4\,h}$, respectively), and absolute BG concentrations ($BG_{0.5\,h}$ through $BG_{4\,h}$). The venous BG values measured with the Super-GL analyzer were used as raw data for statistical analysis. Computations of areas under the BG and serum insulin profiles were based on the linear trapezoidal rule and actual sampling time points.

All statistical analyses for PK and PD were performed using the Statistical Analysis System (SAS), version 9.1 (SAS Institute, Cary, NC). Least square means for most PD endpoints were estimated using a linear mixed effects model with fixed effects for treatment, period, sequence, and their interaction and a random effect for subject. Treatment differences were compared using a one- or two-sided Fisher's Least Significance Difference Test at the 95% confidence interval for pairwise comparisons. Non-normally distributed data were log-transformed. In addition, BG AUCs and BG concentrations were analyzed with analysis of variance as well as analysis of covariance with baseline AUC as covariate. Results of baseline-adjusted analyses did not differ from unadjusted analyses, and results of unadjusted analyses are reported herein. The time parameters for the PD endpoints were analyzed using Hodges and Lehmann point estimates with respective confidence intervals. Power calculations revealed that a sample size of 27 would provide 90% power to detect a 15% difference in both BG AUC and $BG_{max}$ between treatments at a significance level ($\alpha$) of 0.05 (two-tailed).

**PK.** Secondary PK endpoints, determined at predefined times or time intervals through 4 h after the meal, included the AUCs for insulin concentration–time curves (INS $AUC_{0–0.5\,h}$ through INS $AUC_{0–4\,h}$), the maximum insulin concentration ($INS_{max}$), the time to $INS_{max}$ ($tINS_{max}$), and relative (ID vs. SC) bioavailability. PK endpoints were evaluated using a similar mixed effects linear model. In addition, PK endpoints derived from raw insulin concentrations as well as from baseline-adjusted insulin concentrations were analyzed with analysis of variance. Because different assay methods were used for RHI versus IL concentration determinations (chemiluminescence vs. radioimmunoassay, respectively), comparisons of AUCs and maximum concentrations were made only between the same insulin types when dosed at equivalent times. The PK time parameters of either insulin type or route, but given at equivalent premeal times, were analyzed for statistical differences using Hodges and Lehmann point estimates with respective confidence intervals.

### *Safety*

Safety endpoints included the number of adverse events, the number of patients with Draize scale ratings of 4 for erythema or edema, and mean patient ratings of comfort/pain on the VAS after administration. In addition, incidents of hypoglycemia were summarized. As they were anticipated events, neither Draize scale ratings of 4 nor incidents of hypoglycemia were included in adverse-event reports. Safety data were summarized with descriptive statistics.

## Results

### *Patient demographics*

Thirty male patients with T1DM and a mean age of 35 years (range, 19–54 years) were randomized to a treatment sequence. Most patients were white ($n = 28$); two were black. Mean body mass index was 25.7 $kg/m^2$ (range, 18.7–31.7 $kg/m^2$), and mean HbA1c was 7.4% (range, 5.9–8.9%). One patient withdrew consent after the first treatment day for personal reasons. PK and PD analyses were conducted with data from the 29 patients who completed all treatment days. Safety summaries included all 30 patients randomized to a treatment sequence.

### *Mean blood insulin and BG profiles*

Figures 1 and 2 show the mean blood insulin and BG profiles for insulin delivered at −17 min and −2 min premeal, respectively. Based on visual inspection of concentration–time profiles, the best PPG control was achieved with IL administered SC or ID 2 min before the meal and RHI administered ID 17 min before the meal. These three treatments had similar total BG AUCs and BG maxima.

### *PD endpoints: hypothesis testing based on primary endpoint of BG $AUC_{0–1.5\,h}$ (Table 2)*

**Hypothesis 1: ID insulin PPG control is better versus SC for either insulin type when administered at equivalent times.** PPG as measured by BG $AUC_{0–1.5\,h}$ after ID injection of IL was lower than after SC injection when both were given at −2 min, but not significantly ($P = 0.10$). However, BG $AUC_{0–1.5\,h}$ was significantly lower for ID RHI versus SC when both were administered at −17 min ($P = 0.0001$).

**Hypothesis 2: ID administration renders RHI PPG similar to SC IL when administered at equivalent times.** BG $AUC_{0–1.5\,h}$ had nearly identical means without a significant difference

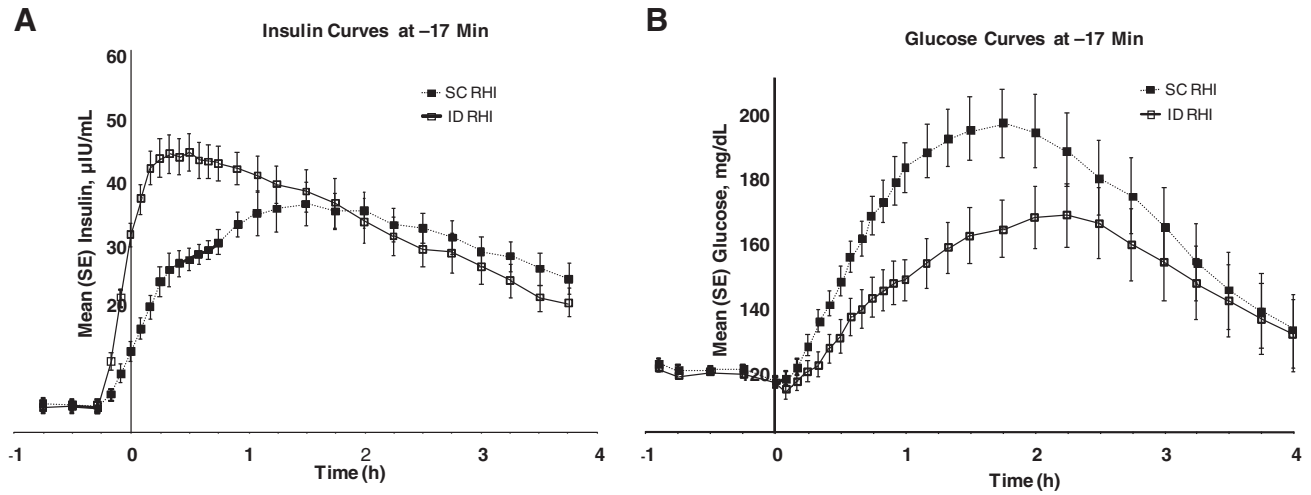


**FIG. 1.** (**A**) Mean ± SE insulin concentration–time profiles for intradermal (ID) and subcutaneous (SC) regular human insulin (RHI) administered 17 min premeal at 0.125 U/kg to 29 type 1 diabetes mellitus patients. (**B**) Corresponding mean ± SE blood glucose response profiles after ingestion of an 82-g carbohydrate liquid meal at $t = 0$.

($P = 0.8345$) between ID RHI and SC IL administered at −2 min, so similarity was confirmed.

Hypothesis 3: ID administration affords similar PPG between RHI and IL, making both insulin types equally effective when given at equivalent times. BG $AUC_{0–1.5\,h}$ was lower for ID IL than ID RHI when both were administered at −2 min ($P = 0.0782$). For this comparison, the threshold for not rejecting similarity was $P \geq 0.1$, so the PPG equivalence between ID insulin types could not be confirmed.

Hypothesis 4: RHI PPG is better with earlier ID administration before a meal. RHI BG $AUC_{0–1.5\,h}$ was significantly lower when administered intradermally at −17 min than at −2 min ($P = 0.0006$), confirming the advantage of earlier administration of ID RHI.

The results and trends noted for secondary PD endpoints were generally consistent with the findings from the primary endpoint of BG $AUC_{0–1.5\,h}$ (Table 3), although some differences existed.

### *PK*

Preprandial insulinemia was similar across all five treatments. The SC profiles of both RHI and IL were as expected. SC RHI had the slowest and most extended absorption of all dosing profiles examined. Serum insulin concentration–time profiles indicated that, when given at the same times, both IL and RHI were more rapidly absorbed when administered intradermally compared with subcutaneously. ID RHI showed approximately a median 1.25 h faster onset, and ID IL was approximately 0.5 h faster for peak systemic exposure than their respective SC comparators. Similarly, both insulin types showed significantly higher early-phase serum insulin concentrations and increased relative bioavailability for ID versus SC dosing. In the first 30 min after injection, insulin

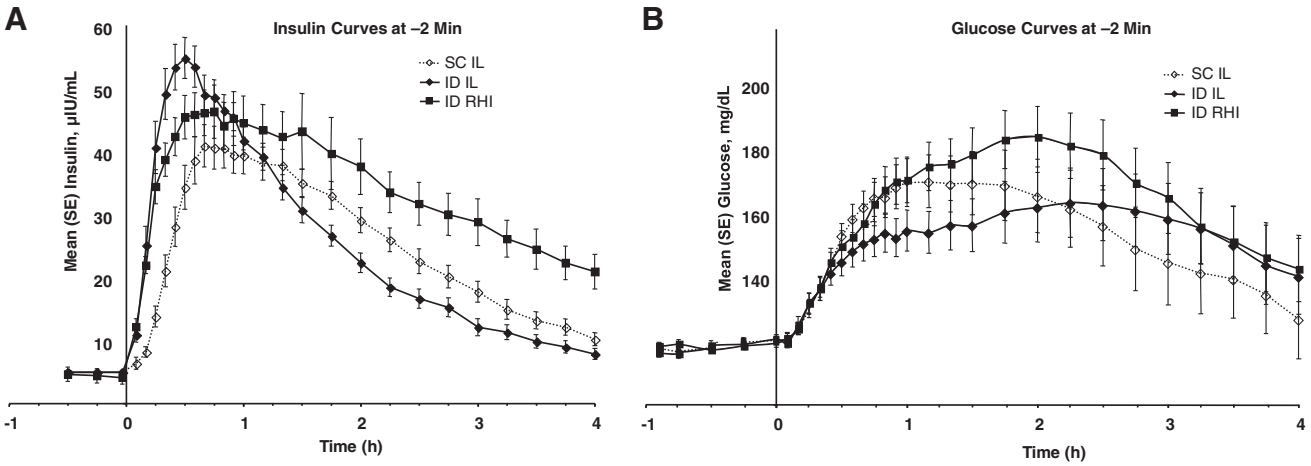


**FIG. 2.** (**A**) Mean ± SE insulin concentration–time profiles for intradermal (ID) insulin lispro (IL), ID regular human insulin (RHI), and subcutaneous (SC) IL administered 2 min premeal at 0.125 U/kg to 29 type 1 diabetes mellitus patients. (**B**) Corresponding mean ± SE blood glucose response profiles after ingestion of an 82-g carbohydrate liquid meal at $t = 0$.

Table 2. Hypothesis Testing Based on Primary Pharmacodynamics Endpoint, Blood Glucose Area Under the Curve for 0–1.5 h, in 29 Patients with Type 1 Diabetes Mellitus on Five Treatment Days with Ingestion of a Standardized Meal

| *Hypothesis* | *Comparison outcome* | *Arms compared* | *Least square mean* | *Confidence interval* | P *value* |
|---|---|---|---|---|---|
| #1A: ID insulin PPG control is better versus SC for IL when administered at equivalent times. | Not confirmed | ID IL −2 min vs. SC IL −2 min | −12.57* | −27.559, 2.411 | 0.0991 |
| #1B: ID insulin PPG control is better versus SC for RHI when administered at equivalent times. | Confirmed | ID RHI −17 min vs. SC RHI −17 min | 33.56* | 18.502, 48.618 | < 0.0001 |
| #2: ID administration renders RHI PPG similar to SC IL when administered at equivalent times. | Confirmed | ID RHI −2 min vs. SC IL −2 min | 1.01† | 0.952, 1.066 | 0.8345 |
| #3: ID administration affords similar PPG between RHI and IL, making both insulin types equally effective when administered at equivalent times. | Not confirmed | ID IL −2 min vs. ID RHI −2 min | 0.94† | 0.889, 0.996 | 0.0782‡ |
| #4: PPG for ID RHI administration is better with earlier versus later administration before a meal. | Confirmed | ID RHI −2 min vs. ID RHI −17 min | 25.15* | 12.551, ∞ | 0.0006 |

The same insulin dose (0.125 U/kg) was administered on all treatment days. Area under the curve units are (mg/dL.h).
*Least square mean of differences between treatments.
†Geometric least square mean of ratios of treatments.
‡For this comparison, based on a two-sided $t$ test and an $\alpha$ level 0.1, the threshold for not rejecting similarity was $P \geq 0.1$.
ID, intradermal; IL, insulin lispro; PPG, postprandial glucose; RHI, regular human insulin; SC, subcutaneous.

AUC was increased more than 100% for either insulin and remained 50% or 70% higher, respectively, for ID IL and ID RHI in the first hour after dosing. Likewise, corresponding mean $INS_{max}$ values were 25% and 35% higher for ID IL and ID RHI, respectively (Table 4 and Fig. 2). Although early ID postprandial bioavailability was markedly higher for either insulin, total bioavailability was similar to that with SC administration across the full 4-h postmeal period. The systemic exposure profile for ID RHI was similar for both the −17 and −2 min dosing arms, when adjusted for differences in dose timing.

### *Safety*

Adverse events ($n = 4$; two events of headache and two events of diarrhea) were reported in three patients. None of these adverse events was considered serious. Four hypoglycemic episodes occurred in three patients, all with insulin administered 2 min premeal: in one patient after SC IL, in a second patient after ID IL, and in a third patient after both SC IL and ID RHI.

A Draize-4 edema reaction (papule formation ≥2 mm in diameter) at the administration site was observed in two patients: one after ID administration of IL and a second after ID RHI. The mean ± SD VAS pain score for all combined ID administrations was higher than that for all SC administrations (6.6 ± 3.9 vs. 4.1 ± 3.3); non-normal distribution prevented detection of statistical significance between routes. However, mean pain scores for both ID and SC administration were less than the VAS midpoint (7.5), which was specified as the pain of the patient's usual insulin injection method.

## Discussion

Microneedle-based ID injection delivers drugs directly to the vicinity of the dermal vascular and lymphatic networks that mediate uptake and distribution and results in significantly faster PK for both RHI and IL than traditional SC administration.[14–16] The $t_{max}$ values for IL or RHI were shortened by approximately 50% and 70%, respectively, relative to SC administration. This study also demonstrates several other important PK/PD differences associated with ID delivery of both IL and RHI. First, ID RHI given 17 min before a liquid meal significantly lowered PPG compared with SC RHI by 14% when measured by BG $AUC_{0–1.5h}$ and by 17% when measured by absolute $BG_{1.5h.}$ Decreased ID RHI BG AUC was observable for the entire 4-h postprandial sampling period, and $BG_{max,\ 0–1.5h}$ was reduced from 201 to 171 mg/dL, a clinically relevant effect. Although ID IL did not exhibit statistically significant differences from SC IL at −2 min for most PD endpoints, similar favorable BG trends were noted. ID IL

Table 3. Pharmacodynamic Endpoints Derived from Postprandial Glycemic Excursions

| | | | | ID RHI | |
|---|---|---|---|---|---|
| | *ID IL (t = −2 min)* | *SC IL (t = −2 min)* | *SC RHI (t = −17 min)* | *t = −17 min* | *t = −2 min* |
| Arithmetic mean ± SD | | | | | |
| BG $AUC_{0–0.5\,h}$ (mg/dLh) | 65 ± 7 | 66 ± 6 | 64 ± 7* | 60 ± 8 | 65 ± 7* |
| BG $AUC_{0–1.5\,h}$ (mg/dLh) | 218 ± 37 | 231 ± 41 | 242 ± 43* | 208 ± 43 | 234 ± 43* |
| BG $AUC_{0–2\,h}$ (mg/dLh) | 299 ± 61† | 314 ± 68 | 340 ± 69* | 289 ± 65 | 324 ± 64* |
| BG $AUC_{0–4\,h}$ (mg/dLh) | 610 ± 171 | 603 ± 196 | 665 ± 187* | 593 ± 173 | 651 ± 175* |
| $BG_{0.5\,h}$ (mg/dL) | 145 ± 23 | 153 ± 20 | 147 ± 24* | 130 ± 27 | 150 ± 26* |
| $BG_{1.5\,h}$ (mg/dL) | 156 ± 45† | 167 ± 54 | 194 ± 53* | 161 ± 46 | 178 ± 45* |
| $BG_{2\,h}$ (mg/dL) | 162 ± 59† | 163 ± 62† | 194 ± 61* | 167 ± 53 | 184 ± 51* |
| $BG_{4\,h}$ (mg/dL) | 143 ± 56 | 129 ± 62 | 132 ± 61 | 130 ± 60 | 140 ± 64 |
| $BG_{max,0–1.5\,h}$ (mg/dL) | 173 ± 35† | 185 ± 41 | 201 ± 48* | 171 ± 40 | 190 ± 40* |
| $BG_{max,0–2\,h}$ (mg/dL) | 181 ± 45 | 189 ± 45 | 208 ± 52* | 179 ± 45 | 197 ± 44* |
| $BG_{max,0–4\,h}$ (mg/dL) | 188 ± 49 | 190 ± 47 | 210 ± 52* | 186 ± 48 | 203 ± 50* |
| $BG_{min,0–1.5\,h}$ (mg/dL) | 113 ± 11 | 114 ± 11 | 112 ± 11* | 106 ± 15 | 115 ± 8* |
| $BG_{min,0–2\,h}$ (mg/dL) | 112 ± 13 | 112 ± 13 | 111 ± 12* | 105 ± 15 | 115 ± 8* |
| $BG_{min,0–4\,h}$ (mg/dL) | 103 ± 24 | 94 ± 29‡ | 95 ± 25 | 94 ± 23 | 99 ± 28 |
| $(BG_{max} - BG_{min})_{0–1.5\,h}$ (mg/dL) | 60 ± 30 | 70 ± 36 | 89 ± 44* | 65 ± 31 | 75 ± 36 |
| $(BG_{max} - BG_{min})_{0–2\,h}$ (mg/dL) | 69 ± 40 | 77 ± 39 | 97 ± 47* | 74 ± 35 | 81 ± 40 |
| $(BG_{max} - BG_{min})_{0–4\,h}$ (mg/dL) | 84 ± 40† | 96 ± 32 | 115 ± 36* | 92 ± 32 | 105 ± 36 |
| Median | | | | | |
| $tBG_{max,0–1.5\,h}$ (h) | 0.83† | 1.00 | 1.50 | 1.33 | 1.17 |
| $tBG_{max,0–2\,h}$ (h) | 1.33 | 1.17 | 1.50 | 1.75 | 1.33 |
| $tBG_{max,0–4\,h}$ (h) | 2.25 | 1.17 | 1.50 | 2.00 | 1.75 |
| $tBG_{min,0–1.5\,h}$ (h) | 0.17 | 0.08 | 0.08 | 0.17 | 0.08 |
| $tBG_{min,0–2\,h}$ (h) | 0.17 | 0.13 | 0.08 | 0.17 | 0.08 |
| $tBG_{min,0–4\,h}$ (h) | 0.25 | 2.75 | 0.42 | 0.33 | 0.25 |

*$P < 0.05$ versus ID RHI −17 min.
†$P < 0.05$ versus ID RHI −2 min.
‡$P < 0.05$ versus ID IL −2 min.

AUC, area under the curve; BG, blood glucose; $BG_{max}$ and $BG_{min}$, maximum and minimum BG concentration, respectively; ID, intradermal; IL, insulin lispro; RHI, regular human insulin; SC, subcutaneous; $tBG_{max}$ and $tBG_{min}$, time to maximum and minimum BG concentration, respectively.

demonstrated a decreased mean absolute BG over the first 2 h postmeal, followed by a relatively static BG profile at later time points. ID IL BG AUC was lower for the first 2 h, but similar by the 4-h time point. Maximum BG in the first 90 min with ID IL was 173 mg/dL compared with 185 mg/dL for SC IL. Factors potentially precluding the ability to statistically demonstrate better PPG control with ID IL include the brief interval between injection and ingestion of 82 g of simple carbohydrate. Also, the weight-normalized insulin dosing strategy did not take into account individual insulin sensitivity, thus increasing the intersubject BG response variability within dosing groups. Visual inspection of the mean PD results suggests a flatter later-phase PPG profile at $t > 2$ h for ID IL, although the basis for this BG persistence is unknown. One possibility is the faster clearance of ID IL from systemic circulation. Further studies are needed to assess whether this relatively flat BG profile can be maintained at a higher insulin dose with less risk of hypoglycemia than with SC injections and whether BG trends for ID IL can be statistically differentiated by better accounting for individual insulin sensitivity.

Second, ID RHI had PPG effects similar to those of SC IL. Microneedle delivery, in effect, made RHI function as effectively as analog insulin, especially in the early postprandial time points. This finding has obvious implications from both clinical and health-economics perspectives and needs additional clinical confirmation. Third, it could not be demonstrated that ID delivery provides equivalent responses between both insulin types, RHI and IL, for PK and for PPG control. It appears that both the faster absorption of the IL analog and the longer terminal elimination phase of RHI are sustained when the insulin is administered intradermally. Fourth, time-based effects of ID dosing are observed because ID RHI produced a greater PPG reduction when given 17 min versus 2 min before the meal. Additional study is necessary to determine the optimal preprandial timing for ID insulin.

These findings indicate that IL or RHI delivered ID with a steel microneedle in patients with T1DM confers a potentially clinically relevant advantage versus SC delivery with respect to postprandial metabolic control. These results corroborate and extend the previous observations of more rapid insulin absorption and more rapid onset of action from microneedle-based ID administration in both a porcine model[14] and in healthy volunteers under euglycemic clamp conditions.[16]

ID delivery via microneedle likely changes the PK and PD of insulin through altered uptake and distribution. The dermis contains dense beds of vascular capillaries and lymphatic vessels that may transport and distribute microneedle-delivered drugs into systemic circulation.[14] Direct delivery to the immediate vicinity of these dermal vascular and lymph networks is thought to be responsible for the rapid absorption properties of intradermally administered insulin,[14,15] and their relative roles in mediating uptake are currently being assessed.

Microneedle delivery of IL and RHI was safe and generally well tolerated in this study, although mean VAS pain scores

Table 4. Pharmacokinetic Endpoints

| | | | | ID RHI | |
|---|---|---|---|---|---|
| | *ID IL (t = −2 min)* | *SC IL (t = −2 min)* | *SC RHI (t = −17 min)* | *t = −17 min* | *t = −2 min* |
| Arithmetic mean ± SD | | | | | |
| INS $AUC_{0–0.5\,h}$ (h$\mu$U/mL) | 17 ± 8 | 8 ± 4* | 9 ± 4† | 19 ± 7 | 13 ± 5 |
| INS $AUC_{0–1\,h}$ (h$\mu$U/mL) | 42 ± 14 | 28 ± 12* | 22 ± 8† | 38 ± 13 | 33 ± 13 |
| INS $AUC_{0–1.5\,h}$ (h$\mu$U/mL) | 60 ± 18 | 47 ± 18* | 38 ± 16† | 56 ± 19 | 53 ± 22 |
| INS $AUC_{0–2\,h}$ (h$\mu$U/mL) | 73 ± 21 | 63 ± 21* | 53 ± 23† | 72 ± 25 | 71 ± 33 |
| INS $AUC_{0–4\,h}$ (h$\mu$U/mL) | 100 ± 29 | 99 ± 30 | NA | NA | 119 ± 57 |
| $INS_{max}$ ($\mu$U/mL) | 59 ± 18 | 47 ± 17* | 35 ± 18† | 47 ± 20 | 49 ± 28 |
| Median | | | | | |
| $t INS_{max}$ (h) | 0.50 | 0.96*‡ | 1.75† | 0.50 | 0.75 |
| $t½INS_{max}$ rising (h) | 0.20 | 0.37 | 0.20 | −0.05 | 0.22 |
| $t½INS_{max}$ falling (h) | 1.45 | 2.40 | 2.62 | 2.66 | 3.18 |

Patients ($n = 29$) with type 1 diabetes mellitus received insulin lispro (IL) or regular human insulin (RHI) (0.125 U/kg) 2 min or 17 min before ingestion of a standardized meal at $t = 0$. Endpoints for IL are derived from unadjusted blood glucose concentrations; endpoints for RHI are derived from baseline-adjusted glucose concentrations.

*$P < 0.05$ versus ID IL −2 min.

†$P < 0.05$ versus ID RHI −17 min.

‡$P < 0.05$ versus ID RHI −2 min.

AUC, area under the curve; ID, intradermal; INS, insulin; $INS_{max}$, maximum INS concentration; $t INS_{max}$, time to maximum INS concentration; $t½INS_{max}$, time to half-maximal INS concentration; NA, not applicable; SC, subcutaneous.

were slightly higher with ID than SC administration. Notably, the mean pain scores for both ID and SC delivery were less than the scale midpoint, which represented the pain of the patient's usual insulin injection. The clinical relevance of the difference in pain scores in this study remains to be determined. In a study of IL delivered by steel microneedles (1.25–1.75 mm long) in 10 healthy volunteers, no participants reported injection-associated pain. That study did not include a VAS-style questionnaire and utilized syringe-like devices with which patients had some familiarity[16] rather than the infusion pump and microneedle catheter set used in the current study. The use of the questionnaire and the unfamiliar administration method may have artificially heightened patients' perceptions by focusing their attention on the administration procedure. Additional studies with sufficient powering to differentiate subjective pain responses are needed to better understand these outcomes.

The study should be interpreted in the context of its methods. First, the insulin dose for each patient was calculated based on body weight and was the same for each patient across treatment days. This weight-normalizing approach, which does not account for patients' insulin sensitivity, contributed to intersubject PPG variability. The benefits of ID insulin administration may be enhanced when prandial doses are titrated to individual patients' needs, as in clinical practice. Second, the liquid meal with standardized carbohydrate content was not representative of patients' actual eating experiences: the entire liquid meal with high simple carbohydrate levels was ingested within 3 min. Third, a tightly controlled preprandial metabolic status was used to control sources of variability and enhance the ability to detect treatment differences but does not mimic patients' typical prandial BG status. Additionally, an open-label study design was chosen because of the impracticality of conducting a double-blinded delivery route study. This design allowed for potential bias in patients' subjective ratings of ID and SC administration pain. However, the main variables of interest—namely, BG and serum insulin concentrations—were not subject to such influences. Further clinical evaluation with more realistic meal types and individualized dosing regimens is underway.

This study expands the clinical insulin response data for steel microneedle delivery by being the first to describe the metabolic effects of two insulin preparations administered intradermally in patients with T1DM. These steel microneedles differ from the borosilicate microneedle systems recently reported for insulin delivery to two adults with T1DM.[18] Notably, steel microneedles are constructed of standard approved medical materials, are not susceptible to breakage, exhibit no leakage, and require simple perpendicular insertion to reach the target 1.5 mm ID delivery depth, rather than the drilling procedure reported for insertion of borosilicate microneedles.[18]

Several topics warrant investigation in future research. In the current study, insulin was rapidly infused rather than injected. Insulin absorption and action are not expected to differ meaningfully between these two approaches, but this expectation remains to be confirmed. Intrasubject reproducibility of ID insulin metabolic effects needs further study. Metabolic predictability might be increased with ID administration over SC, as both intra- and inter-individual dermal thickness variation is much less than for the SC adipose layer,[19] the target for traditional insulin injection, or for other reasons. Additional studies should address the practicality of routine ID administration by patients, clinical metabolic control benefits as discussed previously, and tissue tolerability and immunogenicity with chronic use. In conclusion, these findings indicate a beneficial effect of ID insulin administration compared with traditional SC injection on insulin PK and on postprandial glycemic excursions for both IL and RHI. Further studies are warranted for this promising microneedle-based technology.

## Acknowledgments

The authors acknowledge Jane Saiers, Ph.D. (The Write-Medicine, Inc.) for assistance with writing this manuscript. Becton Dickinson funded Dr. Saiers' work.

### Author Disclosure Statement

The study reported in this manuscript was funded by Becton Dickinson. R.J.P., L.H., D.E.S., and N.G.H. are employed by BD Technologies or BD Medical.

### References

1. Giugliano D, Ceriello A, Razzoli E, Esposito K: Defining the role of insulin lispro in the management of postprandial hyperglycaemia in patients with type 2 diabetes mellitus. Clin Drug Investig 2008;28:199–210.
2. Gerich JE: Clinical significance, pathogenesis, and management of postprandial hyperglycemia. Arch Intern Med 2003;163:1306–1316.
3. Haffner SM: The importance of hyperglycaemia in the nonfasting state to the development of cardiovascular disease. Endocr Rev 1998;19:583–592.
4. Abbatecola AM, Paolisso G: Plasma glucose excursions in older persons with type 2 diabetes mellitus. J Endocrinol Invest 2005;28(11 Suppl Proceedings):105–107.
5. Gin H, Rigalleau V: Post-prandial hyperglycemia. Postprandial hyperglycemia and diabetes. Diabetes Metab 2000;26:265–272.
6. Monnier L, Lapinski H, Colette C: Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA1c. Diabetes Care 2003;26:881–885.
7. Davidson JA, Parkin CG: Is hyperglycemia a causal factor in cardiovascular disease? Does proving this relationship really matter? Yes. Diabetes Care 2009;32(Suppl 2):S331–S333.
8. Conget I, Gimenez M: Glucose control and cardiovascular disease: is it important? No. Diabetes Care 2009;32(Suppl 2):S334–S336.
9. DeFronzo R: Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58:773–795.
10. Bonora E, Corrao G, Bagnardi V, Ceriello A, Comaschi M, Montanari P, Meigs JB: Prevalence and correlates of postprandial hyperglycaemia in a large sample of patients with type 2 diabetes mellitus. Diabetologia 2006;49:846–854.
11. Heinemann L: Insulin pump therapy: what is the evidence for using different types of boluses for coverage of prandial insulin requirements? J Diabetes Sci Technol 2009;3:1490–1500.
12. Plank J, Siebenhofer A, Berghold A, Jeitler K, Horvath K, Mrak P, Pieber TR: Systematic review and meta-analysis of short-acting insulin analogues in patients with diabetes mellitus. Arch Intern Med 2005;165:1337–1344.
13. Erlinger TP, Brancati FL: Postchallenge hyperglycemia in a national sample of US adults with type 2 diabetes. Diabetes Care 2001;24:1734–1738.
14. Pettis RJ: Microneedle Based Drug Delivery: A Promising Minimally Invasive Method for Parenteral Administration. Drug Delivery Companies Report, Spring/Summer. PharmaVentures, Ltd., Oxford, 2004.
15. Harvey A, Kaestner S, Sutter D, Harvey NG, Mikszta JA, Pettis RJ: Microneedle-based intradermal delivery enables rapid lymphatic uptake and distribution of protein drugs. Pharm Res 2010;28:107–116.
16. Pettis RJ, Ginsberg B, Hirsch L, Sutter D, Keith S, McVey E, Harvey NG, Hompesch M, Nosek L, Kapitza C, Heinemann L: Intradermal microneedle delivery of insulin lispro achieves faster insulin absorption and insulin action than subcutaneous injection. Diabetes Technol Ther 2011;13:435–442.
17. AAMI Standards and Recommended Practices,Vol. 4: Biological Evaluation of Medical Devices: ISO 10993-10:2010, Biological Evaluation of Medical Devices—Part 10: Tests for Irritation and Skin Sensitization. Association for the Advancement of Medical Instrumentation, Arlington, VA, 1997.
18. Gupta J, Felnere EI, Prausnitz MR: Minimally invasive insulin delivery in subjects with type 1 diabetes using hollow microneedles. Diabetes Technol Ther 2009;11:329–337.
19. Gibney MA, Arce CH, Byron KJ, Hirsch LJ: Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. Curr Med Res Opin 2010;26:1519–1530.

Address correspondence to:
*Ronald J. Pettis, Ph.D.*
*BD Technologies*
*21 Davis Drive*
*Research Triangle Park, NC 27709*

*E-mail:* rpettis@bd.com