Dose-Dependent Delay of the Hypoglycemic Effect of Short-Acting Insulin Analogs in Obese Subjects With Type 2 Diabetes

A pharmacokinetic and pharmacodynamic study

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OBJECTIVE — Injected volume and subcutaneous adipose tissue blood flow (ATBF) affect insulin absorption. Pharmacokinetics of short-acting insulin analogs were established by assessing injection of small doses in lean subjects, healthy or with type 1 diabetes. In obese patients, however, daily dosages are larger and ATBF is decreased. This study assessed the kinetics of a short-acting insulin analog in obese subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Euglycemic clamps after subcutaneous lispro injections were performed. Six healthy control subjects received 10 units. Seven obese (BMI 38.3 ± 7.0 kg/m²) subjects with type 2 diabetes received 10, 30, and 50 units. Plasma lispro was measured by specific radioimmunoassay and ATBF by the 133Xe-washout technique.

RESULTS — ATBF was 64% lower in subjects with type 2 diabetes than in control subjects. After 10 units injection, time to lispro plasma peak (T_max) was similar (48.3 vs. 55.7 min; control subjects versus type 2 diabetic subjects), although maximal concentration (C_max)/dose was 41% lower in subjects with type 2 diabetes, with lower and delayed maximal glucose infusion rate (GIR_max: 9.0 vs. 0.6 mg/kg/min, P < 0.0001; 69 vs. 130 min, P < 0.0001, respectively). After 30- and 50-unit injections, T_max (88.6 and 130.0 min, respectively) and time to GIR_max (175 and 245 min) were further delayed and dose related (r² = 0.51, P = 0.0004 and r² = 0.76, P < 0.0001, respectively).

CONCLUSIONS — Absorption and hypoglycemic action of increasing dosages of lispro are critically delayed in obese subjects with type 2 diabetes.
frain from strenuous exercise, alcohol, and caffeine intake for 48 h before each experiment.

The experimental protocol was duly approved by the Research Ethics Committee, conducted according to the Declaration of Helsinki principles, and all subjects signed the consent form.

**Protocol**

Experiments were performed 3 weeks apart in randomized order (10, 30, or 50 units). Subjects with type 2 diabetes were admitted at 8:00 P.M. on the evening preceding each experimental day, after having their evening meal and their usual insulin injection. An intravenous antecubital cannula was inserted into each arm: one for venous sampling and glucose measurements (Beckman Instruments, Diagnostic Systems Group, Brea, CA) and the other for dual administration of human insulin (Toronto R, Novo Nordisk Canada, Mississauga, ON) and dextrose as needed. Plasma glucose level was brought progressively into the normal target range (i.e., 5–6 mmol/l overnight).

Experiments started at 8:00 A.M. Anthropometric data were recorded: height, weight, and body composition by bioelectrical impedance (Tanita, Arlington Heights, IL). Subjects were kept fasting (drinking water permitted) during the entire 8-h clamp study. A venous catheter was retrogradely inserted into the hand of the same arm used for nighttime blood samplings, with the hand kept warm in a heating pad. Euglycemic clamp was performed after subcutaneous injection of lispro, 20 min after interruption of the overnight insulin infusion. Lispro was administered with a pen device (Humaten-Ergo, Eli Lilly Canada, Toronto, ON) with an 8-mm needle (30 G × 0.3 × 8 mm) into subcutaneous adipose tissue 8 cm above the umbilicus and 10 cm from the median line.

Plasma glucose was measured every 5 min to clamp glucose levels between 5 and 6 mmol/l with a 20% dextrose infusion via the antecubital catheter already in place. Blood samples were collected at 10-min intervals for the first 3 h and at 20-min intervals thereafter. Study procedures ended at 4:00 P.M. Subjects received a meal and their usual dose of insulin. They were discharged once glucose stabilized over 6 mmol/l.

Healthy control subjects were admitted on the experimental day at 7:30 A.M., fasting from 8:00 P.M. the prior evening. Each received a single dose 10 units lispro; all other procedures were identical to those described above.

ATBF was measured once, on the first experimental day, in each subject using the gold standard method, i.e., the $^{133}$Xe washout technique, a routinely used technique in our hands (16). Briefly, $^{133}$Xe (Bristol-Myers Squibb Canada, Dorval, Quebec) was injected in the subcutaneous adipose tissue of the abdomen, at the opposite side of the insulin injection site. ATBF was measured quantitatively using a Mediscint System (John Caunt Scientific, Oxford, U.K.).

**Sample analysis**

Blood samples were collected in tubes containing sodium citrate and a protease inhibitor cocktail (Complete, EDTA-free; Roche Diagnostics, Mannheim, Germany). Blood was promptly centrifuged at 4°C, and the resultant plasma aliquots were frozen immediately in liquid nitrogen and stored at −80°C until assaying. Plasma lispro was measured in duplicate with a specific radioimmunoassay kit (Linco Research, St. Charles, MO).

**Calculations and statistical analyses**

Plasma lispro measurements were used to estimate absorption rate constant (ka), maximum plasma concentration ($C_{max}$), time to maximal concentration ($T_{max}$), area under the lispro plasma concentration curve ($AUC_{CL,0-\infty}$), $C_{max}$ to dose ratio ($C_{max}/D$), $AUC_{CL,0-\infty}$ to dose ratio ($AUC_{CL,0-\infty}/D$), volume of distribution (Vz), clearance (Cl), half-life (t½), and mean residence time. Calculations were performed assuming a noncompartmental distribution using the WinNonlin 5.2 software (Pharsight, Mountain View, CA).

Using glucose infusion rate (GIR) versus time data, the maximum glucose infusion rate (GIR$_{max}$), time to maximum glucose infusion rate (tGIR$_{max}$), and total glucose infusion from injection to end of clamp (GI$_{tot}$) were calculated.

The study comprised one experiment in healthy subjects and three in obese subjects with type 2 diabetes; in the latter subjects, 10-unit experiments were used as control for comparison with larger doses. Results not normally distributed, based on the Normal Quintile Plot, were log-transformed for all statistical analyses and reported back-transformed in their original units. Values of $P < 0.05$ were considered significant.

Fisher exact tests, for categorical variables, and unpaired t tests, for continuous variables, were used to compare characteristics between groups. Unpaired t tests were used for comparison between groups of pharmacokinetic and pharmacodynamic variables with 10-unit injections. Repeated-measures ANOVA tests were used to compare differences in pharmacokinetic and pharmacodynamic variables at different dosages in subjects with type 2 diabetes, with Tukey honestly significant difference tests for post hoc multiple comparisons.

For correlations between parameters that were repeatedly assessed at multiple insulin dosages in the same patients, repeated-measures ANOVA tests considering clustering of multiple measurements were used. All adjustments were performed again by multivariate ANOVA tests. Data calculations and statistical analyses were performed using JMP 7.0 software (SAS Institute, Cary, NC).

**RESULTS**

Six healthy subjects and seven obese subjects with type 2 diabetes were enrolled (A1C 8.1 ± 1.2%, duration of diabetes 20.2 ± 8.6 years, insulin therapy 5.1 ± 4.2 years). Subjects with type 2 diabetes participated in all three experiments (10, 30, and 50 units). Their age, BMI, weight, and adiposity indexes were higher although ATBF was blunted (Table 1). Heart rate, blood pressure, and ATBF remained stable in both groups during experiments (data not shown).

After the 10-unit injection, the ratio $C_{max}/D$ was 41% lower ($P < 0.001$) in subjects with type 2 diabetes than in healthy subjects, but when $T_{max}$ was increased, $AUC_{CL,0-\infty}$, $AUC_{CL,0-\infty}/D$, ka, and Cl were similar in both groups. Mean residence time, Vz, and t½ tended to be greater in subjects with type 2 diabetes than in control subjects (Fig. 1, Table 2). After the 30- and 50-unit injections, ka dropped by 60% ($P = 0.035$) and $T_{max}$ was delayed by 33% ($P = 0.118$) and 74 min ($P < 0.001$), respectively. $C_{max}/D$, Cl, Vz, and t½ were not affected by the dose, although mean residence time tended to be greater. $T_{max}$ ($r^2 = 0.51$, $P = 0.0004$), $C_{max}$ ($r^2 = 0.90$, $P < 0.0001$), and $AUC_{CL,0-\infty}$ ($r^2 = 0.94$, $P < 0.0001$) were associated with dosage.

The glucodynamic differences between healthy subjects and type 2 diabetic subjects after 10 units of lispro were considerable (Fig. 2). GIR$_{max}$ and GI$_{tot}$ were, respectively, 7% ($P < 0.0001$) and 4% ($P < 0.0001$) of the value measured in healthy subjects, and tGIR$_{max}$ was prolonged by 1 h ($P < 0.0001$). After the 30- and 50-unit injections, GIR$_{max}$ and GI$_{tot}$ were different from the 10-unit...
values ($P < 0.0001$ for both). After the 50-unit lispro injection, tGIRmax was longer than after the 10- and 30-unit injections ($P < 0.0002$). GIRmax ($r^2 = 0.67$, $P < 0.0001$), GI(tot) ($r^2 = 0.73$, $P < 0.0001$), and tGIRmax ($r^2 = 0.76$, $P < 0.0001$) were strongly correlated with dosage. After the 10-unit injection, the average difference between $T_{max}$ and tGIRmax was 19 min in healthy subjects and 74 min ($P < 0.0007$) in subjects with type 2 diabetes. The gap increased further when subjects received 30 and 50 units (86 and 115 min, respectively).

When GIR was plotted as a function of lispro plasma concentrations, the sequential response-concentration relationship depicted a counterclockwise hysteresis for both healthy subjects and subjects with type 2 diabetes (Fig. 3). In healthy subjects receiving 10 units of insulin, an initial GIR response of 2.22 mg/kg/min was seen with insulin concentrations nearing 40 pmol/l. Thereafter, large increases of insulin concentrations were required to increase GIR, although once the response was triggered, it was maintained while plasma concentrations decreased to 20% of the Cmax. In obese subjects with type 2 diabetes, after a 10-unit injection, much greater concentrations of insulin were required to produce even a minimal effect (e.g., 273 pmol/l of insulin elicited a GIR of 0.1 mg/kg/min). The response later increased abruptly to attain GIRmax when plasma concentrations of insulin were already dropping; once GIRmax was attained, the response decreased linearly with insulin plasma concentrations. The same pattern was observed for 30- and 50-unit injections.

**CONCLUSIONS** — This study characterizes the pharmacokinetic and pharmacodynamic proprieties of the short-acting insulin analog lispro in obese subjects with type 2 diabetes. After low-dose injection (10 units), lispro absorption in subjects with type 2 diabetes was as comparable as in control subjects, although the hypoglycemic effect was blunted. However, both absorption and activity were severely delayed and blunted at higher dosages (30 and 50 units) in subjects with type 2 diabetes, featuring a dose-response effect. Kinetic and dynamic parameters estimated in control subjects confirmed those published elsewhere (2–4) and support the value of our findings.

It has been repeatedly proposed, from correlations with pharmacokinetic parameters, that subcutaneous fat thickness, obesity, and low ATBF reduce insulin absorption (12,13). Conversely, the present study does not confirm these facts when small dosages are administered. Insulin Vz and Cl depend on fat-free mass (17). Conversely, adipose tissue is essentially water free. Therefore, higher fat-free mass and total body water in our subjects with

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**Table 1—Characteristics of study groups**

|                | Healthy subjects | Subjects with type 2 diabetes | $P$  |
|----------------|------------------|-------------------------------|------|
| $n$ (men/women) | 6 (3/3)          | 7 (6/1)                       | 0.266|
| Age (years)    | 23.7 ± 2.4       | 60.3 ± 7.6                    | <0.0001|
| BMI (kg/m²)    | 22.1 ± 1.4       | 38.3 ± 7.0                    | 0.0002|
| Weight (kg)    | 70.0 ± 7.6       | 111.0 ± 14.3                  | 0.0002|
| Fat (%)        | 22.4 ± 7.9       | 32.6 ± 5.1                    | 0.017 |
| Fat mass (kg)  | 15.4 ± 4.5       | 36.5 ± 9.6                    | 0.0005|
| Fat-free mass (kg) | 54.6 ± 10.2       | 74.9 ± 7.7                    | 0.002 |
| Total body water (kg) | 40.0 ± 7.5     | 54.5 ± 5.7                    | 0.002 |
| ATBF (ml/min/100 g tissue) | 4.2 ± 0.7       | 1.5 ± 0.5                     | <0.0001|

Data are means ± SD.
Type 2 diabetes could explain the increment tendency in $V_z$, which should account for the decrease in $C_{\text{max}}$ and $C_{\text{max}}/D$ when comparing with control subjects. Within our obese subjects with type 2 diabetes presenting high daily insulin needs, we indeed expected to observe a blunted pharmacodynamic profile compared with control subjects. Moreover, we showed a dose-dependent delay of $T_{\text{max}}$ and GIR$_{\text{max}}$ at high doses in obese type 2 diabetic subjects. Similar results were found in a study done with healthy subjects using lower lispro doses (18) and in another study using inhaled insulin in subjects with type 1 diabetes (19). These effects observed at lower dose were expected to be more pronounced with higher doses in insulin-resistant subjects. Interindividual variation in insulin requirements was evaluated in overweight subjects with type 2 diabetes (20). The 8-h clamp period was not long enough to determine the entire absorption and action profile of 36 units of regular human insulin. Authors attributed these results to the possible slow insulin absorption in

Table 2—Pharmacokinetic and pharmacodynamic parameters after subcutaneous injection of lispro

|                      | Healthy subjects (10 units) | Subjects with type 2 diabetes (10 units) | Subjects with type 2 diabetes (30 units) | Subjects with type 2 diabetes (50 units) |
|----------------------|----------------------------|------------------------------------------|------------------------------------------|------------------------------------------|
| $ka$ (min)           | 0.0531 ± 0.0236            | 0.0455 ± 0.0242                         | 0.0184 ± 0.0076§                         | 0.0179 ± 0.0091§                        |
| $T_{\text{max}}$ (min) | 48.3 ± 4.1                | 55.7 ± 14.0                             | 88.6 ± 21.9                              | 130.0 ± 46.0¶                          |
| $C_{\text{max}}$ (pmol/l) | 523 ± 42                | 310 ± 28                                 | 808 ± 218                                | 1,313 ± 346#                           |
| $C_{\text{max}}/D$ (liters) | 0.0091 ± 0.0007     | 0.0054 ± 0.0005†                        | 0.0047 ± 0.0012                          | 0.0046 ± 0.0012                        |
| AUC$_{0-\text{inf}}$ (pmol/min/l) | 68,462 ± 17,346   | 60,683 ± 15,191                          | 192,155 ± 46,873¶                       | 372,571 ± 59,578¶                      |
| AUC$_{0-\text{inf}}/D$ (min/l) | 1.190 ± 0.302             | 1.056 ± 0.264†                          | 1.140 ± 0.188                            | 1.296 ± 0.208                          |
| $V_z$ (liters)       | 67 ± 16                   | 118 ± 34                                 | 104 ± 53                                 | 107 ± 46                                |
| $Cl$ (l/min)         | 0.88 ± 0.21               | 0.99 ± 0.22                               | 0.90 ± 0.14                              | 0.79 ± 0.13                             |
| $t\frac{1}{2}$ (min) | 67 ± 15                   | 100 ± 34‡                                | 97 ± 38                                  | 136 ± 72                               |
| Mean resistance time (min) | 119 ± 21               | 180 ± 65                                 | 196 ± 30                                 | 236 ± 49                               |
| $t G_{\text{IRmax}}$ (min) | 69 ± 12                | 130 ± 23‡                               | 175 ± 21                                 | 245 ± 64∥                              |
| $GIR_{\text{max}}$ * (mg/kg/min) | 9.0 (7.1–11.4)          | 0.6 (0.4–0.9)†                           | 2.0 (1.4–2.7)∥                           | 2.5 (1.7–3.7)∥                         |
| $Gl_{\text{max}}$ * (mg/kg) | 2.299 (1.881–2.811) | 92 (49–174)‡                             | 364 (249–533)∥                           | 678 (462–994)∥                         |

Data are means ± SD unless otherwise indicated. There were 10 units administered in healthy subjects and 10, 30, and 50 units in obese subjects with type 2 diabetes. *Geometric means with 95% CI; †$P < 0.001$ compared with healthy controls using unpaired $t$ test; ‡$P < 0.0001$ compared with healthy controls using unpaired $t$ test; §$P < 0.04$ compared with 10 units in subjects with type 2 diabetes using repeated-measures ANOVA; ¶$P = 0.002$ compared with 10 units in subjects with type 2 diabetes using repeated-measures ANOVA; #$P < 0.05$ compared with 30 units in subjects with type 2 diabetes using repeated-measures ANOVA; ¶¶$P = 0.002$ compared with 30 units in subjects with type 2 diabetes using repeated-measures ANOVA.

Figure 2—Glucose infusion rate over 480-min euglycemic clamps after subcutaneous injection of 10 units in healthy subjects (□) and 10 units (■), 30 units (●), and 50 units (▲) in obese subjects with type 2 diabetes.
obese subjects with type 2 diabetes and to decreasing insulin absorption with increasing doses. They also correlated the absorbed insulin amount to daily insulin requirements. Herein, at low dosage, we did not observe a slower absorption of lispro in obese subjects with type 2 diabetes, but indeed confirmed that higher doses have a reduced effect. Thus, in obese subjects with type 2 diabetes, as ours, high insulin needs may account in part for low absorption efficiency with high doses.

As shown in Fig. 3, both groups exhibited a counterclockwise hysteresis, although the magnitude was severely blunted in subjects with type 2 diabetes after 10-, 30-, and 50-unit injections. Meanwhile, GIR remained low compared with control subjects. These findings illustrate the insulin resistance expected in our obese subjects with type 2 diabetes.

Fast prandial rise in plasma and fast action of insulin are both key to adequate postprandial metabolic control. The importance of determining whether short-acting insulin analogs are efficient was recently brought into question (21–23). Several studies (rev. in 22) have noted no or few benefits for these analogs relatively to human insulin in patients with type 2 diabetes as opposed to type 1 diabetes. Recent large studies (24,25) provided no evidence supporting the use of preprandial insulins compared with basal insulins. The prolonged time-action profile of short-acting insulin analogs shown in this study could provide an explanation to why preprandial insulins have not had the expected benefits. In daily life, the delay in pharmacodynamic responses after short-acting analog injections may hamper postprandial metabolic control, especially when large dosages are used.

The limitation of this study relates to the impossibility to distinguish between group and dose effect, since high dosages were not tested in the control group.Testing high dosages in control subjects would indeed require intensive care management.

In summary, this study shows that absorption and hypoglycemic action of short-acting insulin analogs are critically delayed at incrementally larger dosages in obese subjects with type 2 diabetes.

Figure 3—Plot of mean glucose infusion rate as a function of insulin plasma concentrations in healthy subjects receiving subcutaneously 10 units of lispro (○) and in obese subjects with type 2 diabetes receiving 10 units (●), 30 units (□), and 50 units (△) of lispro. Data points are connected in chronological order; as depicted by the arrows, the resulting relationship denotes a counterclockwise hysteresis.

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No other potential conflicts of interest relevant to this article were reported.

M.G.-A. contributed to study concept and discussion, reviewed data, and wrote the manuscript. P.d.S. contributed to discussion and data analysis and reviewed/edited the manuscript. J.-P.B. contributed to discussion and data analysis, and statistics and reviewed/edited the manuscript. E.M. researched ATBF data. P.B. contributed to discussion and data analysis and wrote the manuscript. J.M. contributed to study concept and discussion and reviewed/edited the manuscript. J.-L.A. was the principal investigator, contributed to the study concept and discussion, and wrote the manuscript.

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