Comparison of Lys^{B28},Pro^{B29}-Human Insulin Analog and Regular Human Insulin in the Correction of Incidental Hyperglycemia

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OBJECTIVE — To obtain clinically applicable data on the effects of regular human insulin and the Lys^{B28},Pro^{B29}-human insulin analogue (lispro) on the correction of incidental hyperglycemia.

RESEARCH DESIGN AND METHODS — The insulins were compared in a nonclamped randomized crossover study of 27 male IDDM patients. Hyperglycemia was induced by the withdrawal of the normal evening dose of insulin; the next morning patients fasted and received a single dose of study insulin according to a dosing nomogram. Blood glucose concentration and G_R (a measure of glucose corrected for differences in administered insulin dose: G_R = glucose concentration × BMI × insulin dose^{-1}) were followed for 4 h.

RESULTS — The time courses of blood glucose concentration and G_R were significantly different after regular insulin in comparison with lispro (multiple analysis of variance, $P < 0.001$). At $t = 120$ min, glucose concentrations had decreased 1.4 mmol/l more with lispro than with regular insulin (95% confidence interval [CI] 0.6–2.3, $P = 0.002$). Similarly, G_R had decreased 4.4 mol · kg · IU^{-1} · m^{-5} more with lispro than with regular insulin (95% CI 2.6–6.2, $P < 0.001$). The overall difference in glucose values was 0.87 mmol/l (lispro < regular insulin, $P = 0.036$), and the overall difference in G_R values was 1.96 mol · kg · IU^{-1} · m^{-5} (lispro < regular insulin, P = NS). Unexpectedly, the intrinsic variability of G_R was higher for lispro than for regular insulin.

CONCLUSIONS — The more rapid action of lispro is an advantage in the correction of hyperglycemia, even though actual differences in glucose concentrations are smaller than suggested by previous clamped studies.

The rapid and sufficient correction of incidental hyperglycemia is hampered by the long duration of action of regular human insulin and the inability to predict the effect of a certain amount of regular human insulin on blood glucose levels. The latter problem can largely be attributed to the high inter- and intra-individual variability in the absorption of regular human insulin after subcutaneous injection (1–4).

It would seem theoretically plausible that monomeric insulins, such as the Lys^{B28},Pro^{B29}-human insulin analog (lispro), show less variability in absorption than hexameric regular insulin (5). Such insulins could result in more clinically predictable behavior and possibly even a linear dose-effect relationship. The results of glucose clamp studies by Woodworth et al. (6) and Antsiferov et al. (7) seem to support this hypothesis. However, the practical applicability of these results is difficult to ascertain (5,8,9).

This study was designed to compare the decrease in glucose concentrations after the subcutaneous administration of lispro and regular human insulin in a setting as close as possible to naturally occurring hyperglycemia. By using a well-controlled double-blind cross-over design, we tried to eliminate potential confounding factors.

RESEARCH DESIGN AND METHODS

— This study was approved by the Institutional Ethical Review Board. Informed consent was obtained from all participants. The trial was conducted according to the European Good Clinical Practice guidelines.

A total of 27 healthy male IDDM patients aged 20–65 years with HbA_{1c} <10.0% and BMI ≤27.0 kg/m^2 were studied. Patients with impaired hypoglycemia awareness or severely decreased insulin sensitivity were excluded.

At 2 visits that were at minimum 4 days apart, patients were given either lispro insulin (Humalog, Lilly, Indianapolis, IN) or regular human insulin (Humulin R, Lilly) in a randomized double-blind cross-over design. Patients were asked to skip their last insulin dose before the morning of the study. Since most patients used a basal-bolus regimen, this usually was the NPH insulin dose at 10:30 P.M. Patients took no insulin and remained fasting on the morning of the study. The first glucose sample ($t = 0$ min) was measured, and the dose of insulin was based on this value using a BMI-related nomogram (Table 1).

All injections were administered subcutaneously in the abdomen by the same investigator (F.H.). The injection device was a Becton-Dickinson insulin pen (Grenoble, France) with a 30-gauge 8-mm needle

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G_R, relative measure of glucose; lispro, Lys^{B28},Pro^{B29}-human insulin analog; MANOVA, multiple analysis of variance.

Table 1—*Dosing nomogram*

Glucose range (mmol/l)	Insulin dosage per kg/m²	Absolute dose (IU) of insulin administered by BMI (kg/m²)							
		20	21	22	23	24	25	26	27
05–10	0.1	2	2	2	2	2	2	3	3
10–15	0.2	4	4	4	5	5	5	5	5
15–18	0.3	6	6	7	7	7	7	8	8
18–21	0.4	8	8	9	9	10	10	10	11
21–24	0.5	10	10	11	11	12	12	13	14
24–27	0.6	12	13	14	14	14	15	16	16
27–30	0.7	14	15	15	16	17	17	18	19

(NovoFine, Novo Nordisk, Bagsvaerd, Denmark). The pens were prefilled, blinded, and sealed by the hospital pharmacist.

Venous blood samples were taken at t = 20, 40, 60, 90, 120, 150, 180, 210, and 240 min postinjection. Whole blood glucose was measured using an APEC glucose analyzer (Danvers, MA). HbA_{1c} was measured using high-performance liquid chromatography (Biograd, Anaheim, CA).

Since the insulin dosages were determined by the nomogram, we decided to obtain a relative measure which expresses the fall in glucose in such a way that it corrects for the differences in the BMI and the administered dose. This relative measure of glucose, G_R (mol · kg · IU^{-1} · m^{-5}), was calculated by dividing the glucose values (in millimoles per liter) at all time points by the insulin dose actually administered (in international units) and multiplying this figure with the measured BMI (in kilograms per meters squared).

Data were statistically analyzed using the SPSS computer program.

Differences between the time course of lispro and regular human insulin were evaluated using an analysis of variance with repeated measures. The within-patient variability was defined as the square root of the error variance after the correction for the decrease of the G_R values in time.

RESULTS — The participants had a median age of 34 years (range, 20–60 years), a median duration of diabetes of 8 years (range, 0–30 years), an average HbA_{1c} of 7.7 ± 1.1%, and a BMI of 24.4 ± 1.7 kg/m². Thirteen patients were randomized to the lispro-regular insulin sequence, and fourteen were randomized to the regular-lispro insulin sequence. There were no significant differences in baseline characteristics. The average dose of insulin administered was 7.9 ± 3.5 IU of regular human insulin and 7.9 ± 3.7 IU of lispro.

The initial glucose values for regular human insulin ($[Gluc]_{t=0,reg}$) and lispro ($[Gluc]_{t=0,lis}$) were 16.7 ± 4.7 mmol/l and 16.4 ± 5.4 mmol/l, respectively. Four hours after injection, $[Gluc]_{t=240,reg}$ was 8.7 ± 2.3 mmol/l, and $[Gluc]_{t=240,lis}$ was 8.5 ± 2.5 mmol/l. The average values for glucose concentration are plotted against time in Fig. 1.

The differences in glucose values between regular human insulin and lispro were dependent on time (multiple analysis of variance [MANOVA], $P < 0.001$). Overall, the average difference between $[Gluc]_{reg}$ and $[Gluc]_{lis}$ from t = 0 min to t = 240 min using MANOVA was 0.87 mmol/l (lispro < regular human insulin, 95% CI 0.07–1.68, $P = 0.036$). The average fall in glucose concentration from t = 0 min to t = 120 min was 4.8 mmol/l for regular human insulin and 6.2 mmol/l for lispro (95% CI 0.6–2.3, $P = 0.002$).

At each time point after t = 60 min, a good correlation coefficient was found for the individual fall in glucose concentration plotted against the dose of insulin administered per kilograms per meters squared (all $r \geq 0.89$ and $P < 0.001$) for both regular human insulin and lispro.

The relative measure of glucose, G_R (mol · kg · IU^{-1} · m^{-5}), at t = 0 min was 55.2 ± 12.5 mol · kg · IU^{-1} · m^{-5} for regular human insulin and 54.7 ± 10.2 mol · kg · IU^{-1} · m^{-5} for lispro. At t = 240 min, $G_{R,reg}$ was 30.3 ± 11.9 mol · kg · IU^{-1} · m^{-5} and $G_{R,lis}$ was 31.6 ± 15.1 mol · kg · IU^{-1} · m^{-5}. The average values of G_R are represented in Fig. 2.

Again, differences between regular human insulin and lispro were time-dependent ($P < 0.001$). Overall, the average difference between $G_{R,reg}$ and $G_{R,lis}$ from t = 0 min to t = 240 min using MANOVA was 1.96 mol · kg · IU^{-1} · m^{-5} (lispro < regular human insulin, 95% CI −3.25–7.18, $P = 0.45$). The average fall in G_R from t = 0 min to t = 120 min was 14.9 mol · kg · IU^{-1} · m^{-5} for regular human insulin and 19.3 mol · kg · IU^{-1} · m^{-5} for lispro (95% CI 2.6–6.2, $P < 0.001$).

The within-patient variability of all values of G_R from t = 0 min to t = 240 min was 2.68 mol · kg · IU^{-1} · m^{-5} for regular human insulin and 3.58 mol · kg · IU^{-1} · m^{-5} for lispro. The within-patient variability of the values of G_R from t = 0 min to t = 120 min was 2.25 mol · kg · IU^{-1} · m^{-5}

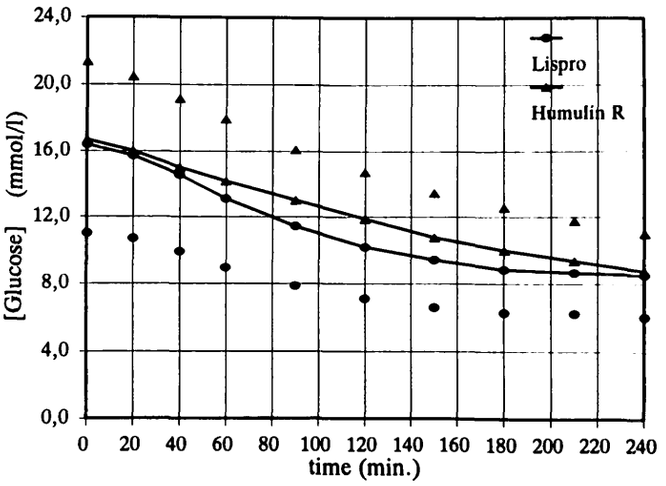

Figure 1—*Glucose concentrations (means ± SD) after the administration of the study insulins according to the nomogram at* t = *0 min.*

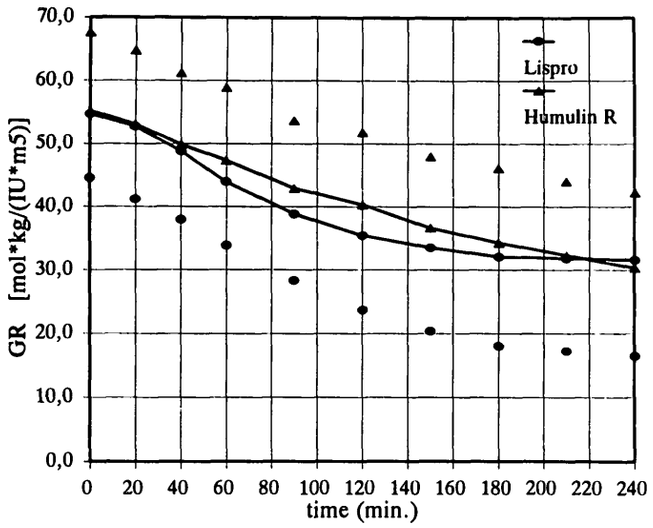

Figure 2—*Values of* G_R *(means ± SD) after the administration of the study insulins according to the nomogram at* t = *0 min.*

for regular human insulin and 2.68 mol · kg · IU^{-1} · m^{-5} for lispro.

The fall in glucose concentration at a given time point that would be the result of the administration of 1 IU insulin per kg/m^2 at t = 0 min can be expressed as ΔG_R. The differential of the fall in G_R against time, $\Delta G_R/\Delta_t$, is a representation of the in vivo time-action profile of the administered insulins (Fig. 3).

CONCLUSIONS — In this study, we used a relative measure of glucose, G_R, that expresses the decrease in glucose concentration per 1 IU/BMI. This mathematical conversion might not be justified if, as published observations indicate (6,10), increased doses of regular insulin result in relatively decreasing effects on glucose disposal. However, we found linear correlations between the administered dose per kg/m^2 and the fall in glucose for regular human insulin and lispro, supporting the feasibility of our approach.

The total decrease in glucose concentration and G_R over 240 min was similar for both insulins, though there seems to be a residual effect of regular human insulin that lasts beyond 240 min (Figs. 2 and 3). The time courses of regular human insulin and lispro were significantly different. As illustrated in Figs. 2 and 3, the effect per IU/BMI in the first 120-min period was significantly higher for lispro than for regular human insulin. Also, the peak effect of lispro, as reflected in $\Delta G_R/\Delta_t$, was about 150% of the peak effect of regular human insulin. These results are compatible with previously published data on lispro (6,7,11–14).

From a clinical point of view, the differences in the decrease of glucose between regular human insulin and lispro are modest: maximally ~1.4 mmol/l at t = 120 min. The overall difference during the whole time period was less (~0.9 mmol/l), while the difference in G_R (~2 mol · kg · IU^{-1} · m^{-5}) was not even significant. Thus, it must be emphasized that large differences in insulin concentrations or glucose infusion rates found in previous clamp studies do not imply similarly large differences in glucose concentration. This may partly explain why the use of lispro, despite its more physiological insulin profile, has not yet led to major improvements in HbA_{1c}.

We unexpectedly found a higher within-patient variability for lispro than for regular human insulin, even when we restricted our analysis to the first 120-min period.

Given the time frame and the randomization procedure used, these differences can hardly be attributed to the residual effects of the patients' own insulin. Maybe the uniformly monomeric state makes the diffusion of lispro more susceptible to subtle changes in local blood flow than the diffusion of regular insulin, which is buffered by the equilibrium mixture of monomeric and polymeric forms. However, given the conflicting results of Antsiferov (7), this point requires further investigation.

In conclusion, as in most other studies, the lispro insulin analog showed a more rapid action profile than regular human insulin. Lispro resulted in lower overall glucose values, but had a higher within-patient variability than regular human insulin. The absolute differences in effect on glucose for regular human insulin and lispro were not very large. Still, the early termination of insulin action is an advantage in the rapid and safe correction of incidental hyperglycemia.

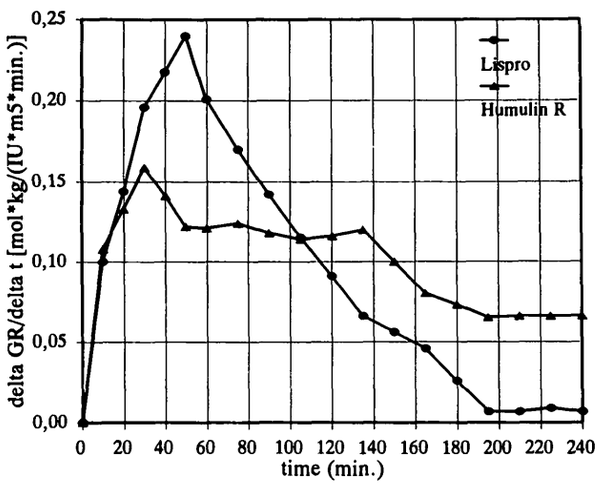

Figure 3—*The differential curve of* ΔG_R *against time,* $\Delta G_R/\Delta_t$, *representing the time-action profiles of the studied insulins.*

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