

Prolonged Efficacy of Short Acting Insulin Lispro in Combination with Human Ultralente in Insulin-Dependent Diabetes Mellitus*

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ABSTRACT

Insulin Lispro is a newly FDA approved analog of human insulin that exhibits rapid absorption and a short duration of action after sc injection. Although Lispro insulin improves immediate postprandial glycemia compared to Regular insulin, long term trials of Lispro insulin have not shown improvement in overall glycemic control, as determined by glycosylated hemoglobin. We hypothesize that this lack of improvement is attributable to the development of late postprandial hyperglycemia secondary to a waning of Lispro insulin's effect in conjunction with continued meal absorption. This study was designed to evaluate the duration of Lispro-induced reductions in plasma glucose after a standardized meal when Lispro insulin is incorporated into a regimen typically employed in insulin-dependent diabetes mellitus.

After establishment of euglycemia overnight, 12 healthy IDDM patients received human Ultralente insulin (0.2 U/kg) alone and in combination with each of the following treatments in random sequence immediately before ingesting a 750-Cal American Diabetes Association breakfast: 1) 0.15 U/kg human Regular insulin (Regular 0.15 group), 2) 0.15 U/kg Lispro insulin (Lispro 0.15 group), 3) 0.1 U/kg Lispro insulin (Lispro 0.1 group), and 4) an equimolar (1:1) mixture of Lispro and Regular insulins (0.15 U/kg; 1:1 Mix group). Glucose and hormonal parameters were assessed for 8 h after the meal.

Peak postprandial glucose was increased in the Regular insulin

group compared to that in all groups that incorporated Lispro insulin ($P < 0.001$). Glucose area under the curve (AUC) was decreased in the Lispro 0.15 group compared to that in the Lispro 0.1 group, and glucose AUC was decreased in the Lispro 0.15 and 1:1 Mix groups compared to that in the group given Regular insulin ($P < 0.001$). Mean plasma glucose concentrations during the final hour of study were increased in the Ultralente group compared with those in all other treatment groups and were increased in the Lispro 0.1 group compared with those in the Regular, Lispro 0.15, and 1:1 Mix groups ($P < 0.05$). Insulin AUC was significantly reduced in the Lispro 0.1 group compared to those in all other short acting insulin groups ($P < 0.001$), and time to peak insulin was more rapid in the two Lispro groups than those in all other treatment groups ($P < 0.01$). The glucagon response was significantly greater in the Ultralente group compared to those with all other treatments. There was no difference in the development of hypoglycemia between the groups.

This study demonstrates that the reductions in plasma glucose effected by Lispro insulin are consistent and stable for 8 h after meal ingestion when Lispro insulin is used in combination with human Ultralente insulin. These findings suggest that improvement in overall glycemia, as assessed by glycosylated hemoglobin, may be achievable with Lispro insulin if adequate doses are administered. (*J Clin Endocrinol Metab* 82: 920–924, 1997)

ACHIEVING normal postprandial glycemia is a difficult, but appropriate, goal in patients with insulin-dependent diabetes mellitus (IDDM) (1). The recent FDA approval of Lispro insulin, which has a rapid onset and short duration of action after sc injection, allows a more physiological delivery of insulin after a meal and has made the achievement of near-normal postprandial glycemia a realistic possibility (2, 3). There may, however, be limitations to the benefits of Lispro insulin. Although published studies have clearly documented Lispro insulin's ability to improve glycemia for 2–4 h after a meal compared to the effect of Regular human insulin, the longer term postprandial effectiveness of Lispro insulin has not been ade-

quately studied (3–8). Moreover, published studies have been unable to demonstrate an improvement in overall glycemic control, as determined by glycosylated hemoglobin, among IDDM subjects who used Lispro insulin compared to those who used human Regular insulin during a year-long trial (6, 8). One possibility for this observation may be that Lispro insulin is unable to suppress late postprandial hyperglycemia secondary to a waning of its pharmacological activity, as it has been demonstrated that meal absorption persists for at least 6 h after ingestion (9).

This study was designed to elucidate the most effective short acting insulin to use in combination with human Ultralente (UL) to suppress hyperglycemia for up to 8 h after ingestion of a standardized meal. We hypothesized that Lispro insulin in combination with human UL would provide superior early postprandial glycemia compared to other short acting insulins, but that these effects would wane and result in late-onset hyperglycemia, especially with low doses of Lispro insulin. Our results suggest that Lispro insulin in combination with human UL is more effective than an equivalent dose of Regular insulin or a reduced dose of Lispro insulin at maintaining glycemia for 8 h after a meal. Additionally, our data suggest that an equimo-

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lar mixture of Lispro and Regular insulins has similar efficacy to Lispro insulin alone.

Subjects and Methods

Study subjects

Twelve IDDM patients were studied on five separate occasions in a prospective, randomized, single blind, cross-over study. All patients were free of the secondary complications of diabetes, were otherwise healthy, and had been receiving insulin therapy for at least 2 yr. Seven men and five women with a mean age of 34.4 ± 3.2 yr were studied. The mean duration of diabetes was 14.4 ± 2.0 yr, and the mean body mass index was 24.0 ± 1.0 kg/m². All enrolled patients had serum C peptide concentrations less than 0.06 ng/mL 60 min after the ingestion of Sustacal (10). All subjects gave informed consent for participation in the study as approved by the University of New Mexico human research review committee.

Study protocol

All subjects participated in five separate 24-h studies in random sequence separated by 7–10 days. All subjects were admitted to the University of New Mexico General Clinical Research Center on the evening before the study, and forearm veins were catheterized for the administration of iv insulin in one arm and the attainment of blood samples in the contralateral arm. All subjects were served a 10 Cal/kg American Diabetes Association (ADA) meal at 1800 h, and euglycemia was established and maintained overnight with a continuous iv infusion of human Regular insulin mixed in 0.45 mol/L saline to a concentration of 0.1 U/mL (10). The insulin infusion was adjusted based on hourly capillary blood glucose (CBG) determination to achieve a target morning plasma glucose concentration of 5.0–7.8 mmol/L (90–140 mg/dL). Intravenous insulin was discontinued at 0730 h the following morning. Subjects were allowed free access to noncaloric beverages during the 24-h hospital admission. Long acting insulin was withheld for 48 h before the study, and intermediate acting insulin was withheld for 24 h before the study.

At 0800 h, all subjects received one of a series of five sc insulin treatments injected into the abdominal wall by study personnel. All short acting insulins were mixed in a syringe with human UL immediately before injection, and subjects were blinded to the treatment received. The five insulin treatments consisted of 1) 0.2 U/kg human UL, 2) 0.2 U/kg UL plus 0.15 U/kg human Regular insulin, 3) 0.2 U/kg UL plus 0.15 U/kg Lispro, 4) 0.2 U/kg UL plus 0.1 U/kg Lispro, or 5) 0.2 U/kg UL plus an equimolar mixture (1:1 Mix) of 0.15 U/kg Lispro and Regular insulins. Immediately after insulin injection, all subjects were served a 750-Cal ADA breakfast (50% carbohydrate, 20% protein, and 30% fat) and were encouraged to finish it within 20 min. For any given subject, all five study breakfasts were identical. Blood was sampled for CBG, plasma glucose, and insulin at 0750 and 0800 h (baseline), and then every 30 min for 8 h after ingestion of the meal. Additional blood was sampled at baseline and then hourly for glucagon, norepinephrine, and epinephrine. CBG results were used only to adjust the overnight insulin infusion and to prevent severe hypoglycemia. No midday meal was provided. If hypoglycemia developed, 25 mL 50% dextrose were administered iv, and the study was continued. Hypoglycemia was defined as a CBG level less than 2.8 mmol/L (50 mg/dL) with typical hypoglycemic symptoms or any CBG measurement less than 2.2 mmol/L (40 mg/dL).

Sample analysis

CBG concentrations were determined with a One Touch II glucose meter (Lifescan, Milpitas, CA). Plasma glucose was assessed using the Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). C Peptide concentrations were assayed using the Incstar RIA kit (Steelewater, MN). Free insulin concentrations for both Lispro and Regular insulin were determined after treatment of the serum with 25% polyethylene glycol using the Coat-A-Count RIA kit (Diagnostic Products Corp., Los Angeles, CA) (11). Displacement curves for Lispro insulin and Regular human insulin were equivalent by statistical analysis with Allfit (12). Serum glucagon concentrations were determined by the General Clinical Research Center core laboratory at Washington University (St.

Louis, MO) using a RIA (13). Samples for plasma catecholamines were placed on ice immediately after sampling and stored at -70 C until being assayed radioenzymatically (14).

Statistical analysis

The primary efficacy variables assessed were 1) overall postprandial glycemia, as determined by total glucose area under the curve using the trapezoidal rule; 2) peak postprandial glucose concentration; and 3) late postprandial glycemia, as assessed by averaging the plasma glucose concentrations from the final hour of study (7, 7.5, and 8 h postprandially) for each subject. Secondary variables included serum free insulin levels, late postinjection insulin concentrations (the average of the free insulin concentrations from the final hour of study for each subject), and counterregulatory hormone determinations. All parameters were compared among the various groups using ANOVA for repeated measures with *post-hoc* application of Student's *t* test for paired data where appropriate. The area under the curve data for glucose were compared for the entire 8-h study using a one-way ANOVA and *post-hoc* Student's *t* testing. The development of hypoglycemia was compared among the groups by Fisher's exact test. All data are reported as the mean \pm SEM.

Results

Postprandial glycemia

Figure 1A depicts the mean postprandial glycemic excursions for all five treatment groups. No studies were discon-

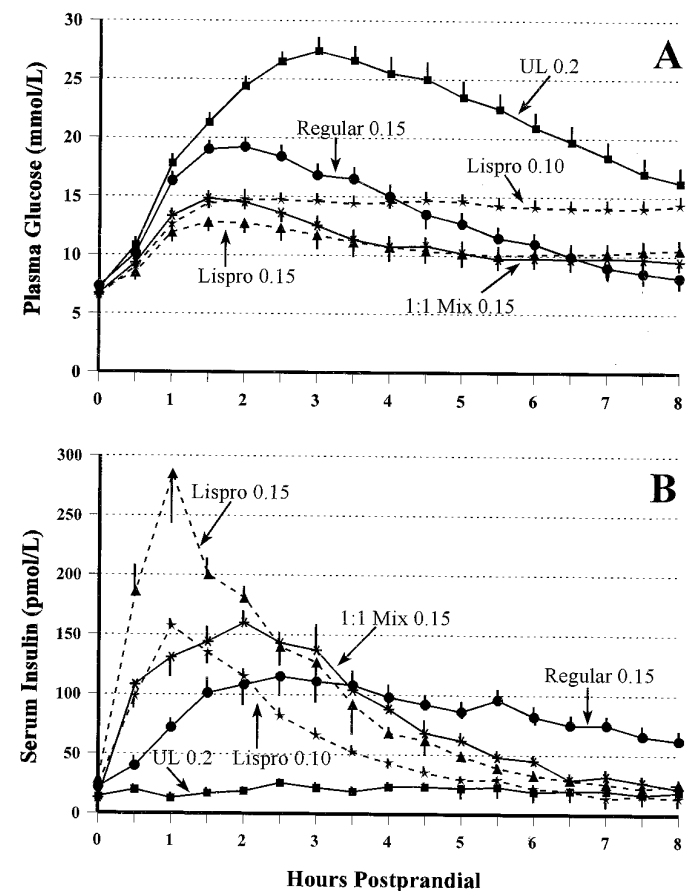


FIG. 1. Plasma glucose (A) and serum free insulin concentrations (B) for 8 h after ingestion of a 750-Cal ADA breakfast. Solid squares represent the 0.2/kg UL group, solid circles represent the UL plus Regular insulin (0.15 U/kg) group, solid stars represent the UL plus Lispro (0.1 U/kg) group, solid triangles represent the UL plus Lispro (0.15 U/kg) group, and asterisks represent the UL plus 1:1 Mix group.

tinued secondary to hypoglycemia. Mean preprandial plasma glucose concentrations did not significantly differ between groups, as follows: UL, 7.1 ± 0.2 mmol/L (128 ± 4 mg/dL); regular, 7.2 ± 0.3 mmol/L (130 ± 6 mg/dL); Lispro 0.1, 6.5 ± 0.3 mmol/L (117 ± 6 mg/dL); Lispro 0.15, 6.9 ± 0.4 mmol/L (125 ± 8 mg/dL); and 1:1 Mix, 6.7 ± 0.3 mmol/L (120 ± 6 mg/dL; $P > 0.05$). The peak postprandial plasma glucose level after UL insulin alone was significantly greater than that for all other treatment groups ($P < 0.001$), and peak plasma glucose concentrations were significantly reduced in the Lispro 0.15, Lispro 0.1, and 1:1 Mix groups compared to that in the Regular insulin group ($P < 0.001$). Similarly, the area under the curve for glucose was increased in the UL group compared to those in all other treatment groups ($P < 0.001$) and was significantly greater for human Regular insulin than for Lispro 0.15, Lispro 0.1, and the 1:1 Mix ($P < 0.001$). Additionally, the glucose area under the curve was greater in the Lispro 0.1 group compared to that in the Lispro 0.15 group ($P < 0.001$). Late postprandial glycemia was increased in the UL group compared with all other treatment groups ($P < 0.001$) and was significantly decreased in the Regular ($P < 0.001$), Lispro 0.15 ($P < 0.05$), and 1:1 Mix ($P < 0.05$) studies compared to the Lispro 0.1 study. Plasma glucose data are summarized in Table 1.

Serum free insulin

Baseline insulin concentrations did not significantly differ among the groups (Fig. 1B). The insulin area under the curve was significantly decreased in the UL group compared to those in all other treatment groups and was also decreased in the Lispro 0.1 group compared to those in all other treatment groups incorporating a short acting insulin ($P < 0.001$). There were no statistically significant differences among the Lispro 0.15, Regular, and 1:1 Mix groups in the insulin area under the curve. As shown in Table 1, the time to peak insulin was significantly more rapid in the Lispro 0.15 and 0.1 groups than in all other treatment groups ($P < 0.001$). There were no significant differences between the UL, Regular, or 1:1 Mix groups with respect to time to peak. Insulin concentrations were elevated in the Regular group during the final hour of study compared to all other treatments (Table 1).

Counterregulatory hormones

Counterregulatory hormone concentrations are shown in Fig. 2. Glucagon concentrations were increased in the UL group compared to those with all other treatments, as shown in Fig. 2A. There were no differences among the groups with respect to plasma concentrations of norepinephrine (Fig. 2B) or epinephrine (Fig. 2C).

Development of hypoglycemia

Hypoglycemia was an infrequent occurrence during this study. Two subjects developed hypoglycemia in the Regular insulin group, compared with three subjects in the 1:1 Mix group and one subject in the Lispro 0.15 group ($P > 0.1$). In all cases, hypoglycemia occurred between 6–7 h after ingestion of the meal.

Discussion

The ability of Lispro insulin to control short term postprandial glycemia more effectively than human Regular insulin in IDDM has been documented in several studies (3–8). These studies are limited, however, by a short period of postprandial assessment (3, 5–8), by the lack of a standardized meal (3, 6, 8) and/or insulin dose (3, 6, 8), and by the lack of provision of a basal, long acting insulin (4, 5, 7). Thus, little is known about the longer term postprandial efficacy of Lispro insulin when it is used in the types of regimens most commonly employed by IDDM patients receiving intensive diabetes management. This study suggests that a single injection of Lispro insulin in combination with human Ultralente has a persistent stabilizing effect on postprandial glycemia for 8 h after the ingestion of a meal. Moreover, this study shows that Lispro insulin has greater efficacy at suppressing postprandial hyperglycemia than an equivalent dose of Regular insulin in this setting.

Previous studies have documented the importance of the timing of preprandial Regular insulin injections in optimizing postprandial glycemia in IDDM (15–17). These reports indicate that Regular insulin should be injected 30–45 min before the ingestion of a meal to suppress postprandial hyperglycemia most effectively. The current study design un-

TABLE 1. Glucose and insulin parameters by treatment group

	UL alone (0.2 U/kg; n = 12)	Regular (0.15 U/kg; n = 12)	Lispro (0.10 U/kg; n = 12)	Lispro (0.15 U/kg; n = 12)	1:1 mix (0.15 U/kg; n = 12)
Glucose AUC (mmol/min·L)	5821 ± 144	3720 ± 85^a	3463 ± 88^a	$2415 \pm 110^{a,b,c}$	$2499 \pm 85^{a,c}$
Peak glucose (mmol/L)	28.1 ± 0.4	20.0 ± 0.3^a	$16.5 \pm 0.2^{a,c}$	$14.5 \pm 0.3^{a,c}$	$15.8 \pm 0.3^{a,c}$
Mean glucose during hour 7–8 (mmol/L)	17.2 ± 5.5	$8.6 \pm 4.2^{a,b}$	$14.1 \pm 3.0^{d,f}$	$10.4 \pm 4.3^{e,f}$	$9.7 \pm 5.1^{e,f}$
Mean free insulin during hour 7–8 (pmol/L)	18.4 ± 4.8	$68.0 \pm 16.0^{e,f,g,h}$	22.3 ± 7.2	24.6 ± 5.9	25.6 ± 4.7
Time to peak insulin (min)	208 ± 134	200 ± 103	$65 \pm 25^{a,c,i}$	$70 \pm 41^{a,c,i}$	115 ± 40

^a $P < 0.001$ vs. Ultralente (0.2 U/kg).

^b $P < 0.001$ vs. Lispro (0.1 U/kg).

^c $P < 0.001$ vs. Regular (0.15 U/kg).

^d $P < 0.05$ vs. Ultralente (0.2 U/kg).

^e $P < 0.01$ vs. Ultralente (0.2 U/kg).

^f $P < 0.05$ vs. Lispro (0.1 U/kg).

^g $P < 0.01$ vs. 1:1 mix.

^h $P < 0.01$ vs. Lispro (0.15 U/kg).

ⁱ $P < 0.001$ vs. 1:1 mix.

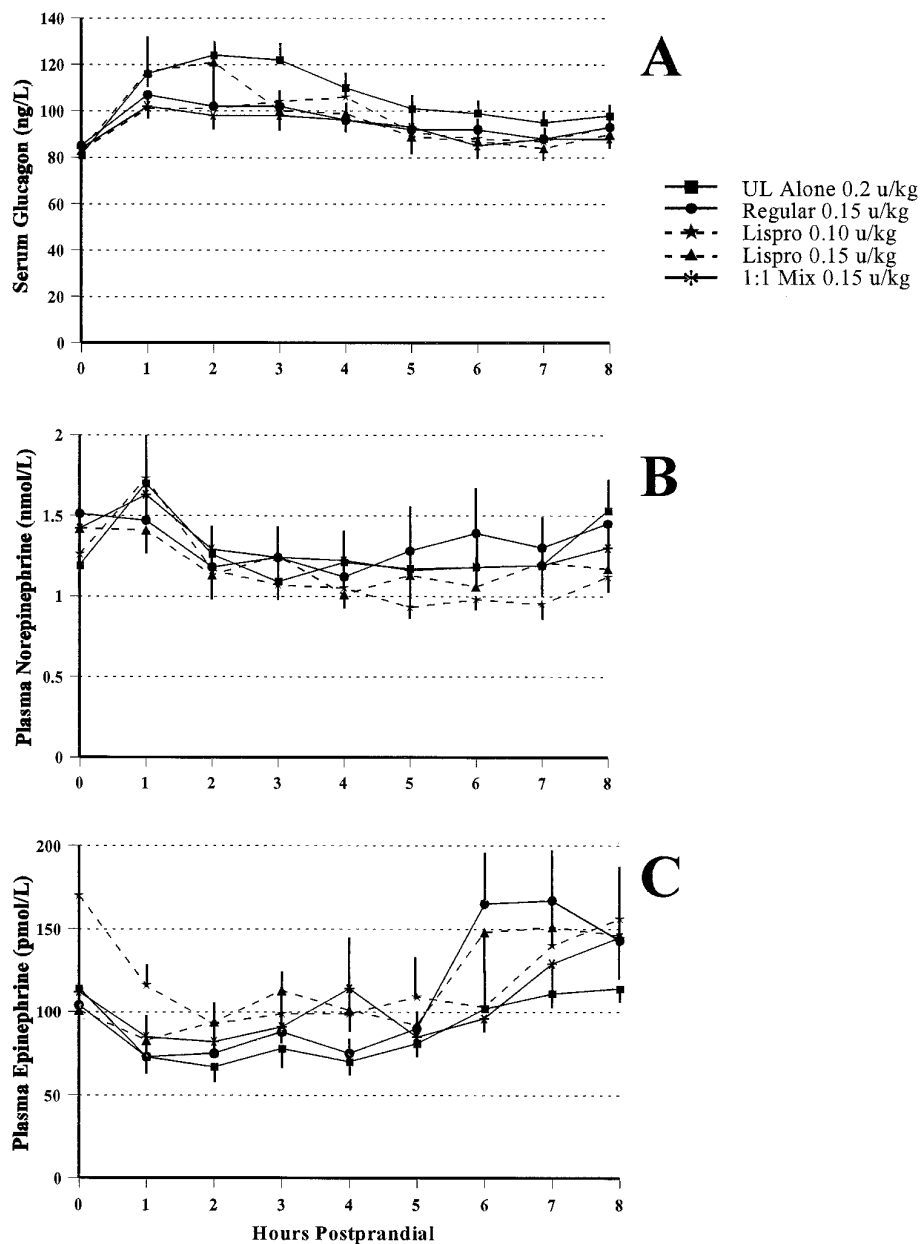


FIG. 2. Serum glucagon (A), plasma norepinephrine (B), and plasma epinephrine (C) concentrations for 8 h after sc insulin injection. *Solid squares* represent the UL (0.2/kg) group, *solid circles* represent the UL plus Regular insulin (0.15 U/kg) group, *solid stars* represent the UL plus Lispro (0.1 U/kg) group, *solid triangles* represent the UL plus Lispro (0.15 U/kg) group, and *asterisks* represent the UL plus 1:1 Mix group.

underscores the importance of the proper timing of administration of human Regular insulin and emphasizes the differences between Lispro insulin and Regular insulin. Additionally, previous studies suggest that Lispro insulin results in reduced short term postprandial glycemia even when the timing of Regular insulin injection is optimized (3–8). Although insulin dosages must be individualized for each patient with diabetes, our chosen sc dosages of 0.2 U/kg UL plus 0.1–0.15 U/kg of a short acting preparation are not different from the dosages typically employed by patients with diabetes (18). Finally, these results apply directly only to those patients who combine a short acting insulin with UL before breakfast.

The low rate of occurrence of hypoglycemia in this study may be an artifact of the relatively large breakfast these patients received. As such, interpretation of the counterregulatory

hormone data is limited by the absence of a sufficient stimulus for counterregulatory hormone secretion. Torlone *et al.* (19) have previously demonstrated that hypoglycemia induced by Lispro insulin results in a counterregulatory hormone response identical to that elicited by human Regular insulin. In the present study, we speculate that the elevated glucagon concentrations observed during the control experiment with UL insulin alone reflect an early manifestation of insulin deficiency (20).

In conclusion, our data suggest that Lispro insulin combined with human UL is an effective regimen for optimizing postprandial glycemia for 8 h after a meal in patients with IDDM, and this regimen confers no increased risk of early postprandial hypoglycemia or late postprandial hyperglycemia. As such, improvement in overall glycemia and glycosylated hemoglobin may be achievable with Lispro insulin

provided that adequate doses of Lispro insulin are administered. Finally, an equimolar mixture of Lispro insulin and Regular insulin is as effective as Lispro insulin alone in controlling postprandial glycemia and may prove to be a cost-effective method of achieving the benefits of Lispro therapy in patients with limited financial resources.

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