Metabolic and Immunologic Effects of Insulin Lispro in Gestational Diabetes

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OBJECTIVE — To compare the immunologic response to insulin lispro with that to regular human insulin, thereby assuring its safety for use in women with gestational diabetes, and to verify that it is effective.

RESEARCH DESIGN AND METHODS — We compared the metabolic and immunologic effects of insulin lispro and regular human insulin in 42 women >18 years of age diagnosed with gestational diabetes by oral glucose tolerance testing at 14–32 weeks of gestation. Patients were randomized to receive regular human insulin or insulin lispro before consuming a test meal. Serum insulin, blood glucose, and C-peptide concentrations were measured. Throughout the remainder of gestation, patients received premeal insulin lispro or regular human insulin combined with basal insulin and performed blood glucose self-monitoring before and after each meal. Insulin antibodies and HbA_{1c} were determined at enrollment and 6 weeks later. In addition, 10 patients received continuous intravenous insulin (4 lispro, 6 regular human insulin) and dextrose infusions intrapartum to assess placental insulin transfer.

RESULTS — Anti-insulin antibody levels were similar in the two groups. Insulin lispro was not detectable in the cord blood. During a meal test, areas under the curve for glucose, insulin, and C-peptide were significantly lower in the lispro group. Mean fasting and postprandial glucose concentrations and end point HbA_{1c} were similar in the two groups. The lispro group demonstrated fewer hypoglycemic episodes (symptoms and blood glucose concentrations <55 mg/dl). No fetal or neonatal abnormalities were noted in either treatment group.

CONCLUSIONS — Insulin lispro may be considered a treatment option for women with gestational diabetes.

Diabetes Care 22:1422–1427, 1999

Infants of women with gestational diabetes have an increased risk of macrosomia, hypoglycemia, hyperbilirubinemia, hypocalcemia, and erythremia (1). Although still controversial, the rate of complications in the neonate has been associated with maternal glucose concentrations (2–4). Perhaps the debate remains because many of the reports claiming that neonatal complications occur in spite of excellent metabolic control fail to measure postprandial glucose concentrations (5–7). Postprandial glucose control has been suggested as essential for a healthy neonate for the patient with gestational diabetes (3,8–10). Some researchers have suggested that neonatal morbidity is secondary to the variability of maternal serum glucose and presence of antibodies to insulin (10,11). Menon and colleagues reported that placental transfer of insulin complexed with immunoglobulin was associated with macrosomia in the fetuses of mothers with near-normal glycemic control during gestation (11). In that study, the antibody-bound insulin transferred to the fetus was proportional to the concentration of antibody-bound insulin measured in the mother. Furthermore, the amount of antibody-bound insulin transferred to the fetus correlated directly with macrosomia in the infant, and was independent of maternal blood glucose concentrations. In contrast, Jovanovic et al. (10) reported that only improved glucose control, as evidenced by lower postprandial glucose excursions, but not lower insulin antibody concentrations, correlated with lower fetal weight. They concluded that, although maternal insulin antibodies to exogenous insulin are probably undesirable, they do not influence infant birth weight.

Recently, it has been reported that insulin lispro, an analog of regular human insulin with a peak insulin action achieved within 1 h after injection, significantly improves postprandial glucose concentrations in nonpregnant diabetic patients (12). The primary objective of this study was to compare immunologic effects of insulin lispro, as a safety concern, with those of regular human insulin in the treatment of patients with gestational diabetes, while at the same time assuring efficacy at least equal to that of regular insulin.

RESEARCH DESIGN AND METHODS

Study design

This study was a randomized open-label parallel-group design, and subjects signed informed consent approved by the Institutional Review Board. A total of 42 women with gestational diabetes diagnosed at 14–32 weeks of gestation using the Carpenter and Coustan modification of the National Diabetes Data Group (NDDG) criteria (13), who failed to obtain adequate glucose control with diet and exercise, were recruited to participate in the study. Adequate glucose control was defined as fasting and preprandial fingerstick blood glucose concentrations <90 mg/dl (5.0 mmol/l) and 1-h postprandial fingerstick blood glucose concentrations <120 mg/dl (6.7 mmol/l) (14–16). Patients who failed to achieve these glucose concentrations in

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Received for publication 12 January 1999 and accepted in revised form 12 May 1999.

L.J. has received honoraria for speaking engagments from Eli Lilly. R.R.B. and E.J.B. hold stock in Eli Lilly.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

>70% of home blood glucose monitor readings obtained during a one-week period were considered to be dietary therapy failures. Patients were excluded if they had received prior treatment with insulin, had pregestational diabetes, or demonstrated significant concurrent organic disease. If the ultrasonic examination documented an anatomically normal fetus, computer-generated random numbers assigned the women to receive either subcutaneous insulin lispro (n = 19) or regular insulin treatment (n = 23). Regular human insulin (Humulin R) and insulin lispro (Humalog) were supplied by Eli Lilly (Indianapolis, IN). All 42 women participated in a standardized meal test but one of the women randomized to regular insulin decided not to continue. The other 41 were maintained on their assigned insulin and followed throughout the remainder of the pregnancy. Because the two insulin preparations need to be injected at different times in relation to the meal, the study was not blinded. The last 10 women who delivered vaginally at term (4 insulin lispro and 6 regular human insulin) were recruited to participate in an intrapartum insulin infusion study.

Baseline blood determinations included HbA_{1c} (normal ranges in pregnancy 3.9–4.7%, coefficient of variation <3%, high pressure liquid chromatography; Primus, Kansas City, MO), chemistry panel, hemoglobin, hematocrit, and anti-insulin antibody binding. Serum samples for antibody determinations were collected, frozen, and then shipped to the central laboratory. The binding capacity of antibodies specific for insulin lispro, regular human insulin, and antibodies recognizing both peptides (cross-reactive antibodies) was determined by a radioimmunoassay (Quest Diagnostics, San Juan Capistrano, CA) (17,18). A positive antibody response was defined as both *1*) a twofold increase in the percent binding from baseline and *2*) the resultant percent bound greater than the upper limit of the normal reference range.

The initial total daily insulin dose was calculated according to the following formula: 0.7 U · kg^{-1} · day^{-1} if insulin therapy was initiated by 21 weeks of gestation; 0.8 U · kg^{-1} · day^{-1} if initiated between 21 and 26 weeks of gestation; and 0.9 U · kg^{-1} · day^{-1} if initiated at 26 weeks of gestation or later. The total daily caloric need was based on each woman's current body weight and was calculated as 30 kcal/kg of current body weight for women whose weight was 80–120% of ideal body weight, 24 kcal/kg of current body weight for a woman who was 121–150% of ideal body weight, and 12 kcal/kg current body weight for a woman who was >150% of ideal body weight.

Table 1—*Patient demographics*

	Insulin lispro	Regular human insulin	*P* value
n	19	23	—
Age (years)	34.2 ± 1.3	29.8 ± 1.0	<0.01
Height (m)	1.57 ± 0.02	1.56 ± 0.01	0.56
Weight (kg)	76.3 ± 2.9	78.5 ± 2.5	0.58
BMI	31.5 ± 1.1	33.3 ± 1.2	0.28
Ethnicity			
Caucasian	2	0	—
Hispanic	17	23	—
Parity	1.4 ± 0.3	1.7 ± 0.3	0.60
Gravidity	1.8 ± 0.2	2.4 ± 0.3	0.14
Weeks of gestation (at enrollment)	27.3 ± 1.4	25.6 ± 1.3	0.37
Prior gestational diabetes			
Yes	1	1	—
No	10	10	—
Unknown	8	12	—

Data are *n* or means ± SEM. Significance was determined by unpaired *t* test.

At randomization, a test meal consisting of 20% of each woman's calculated total daily caloric need was given between 7:30 and 8:30 A.M. following the subcutaneous injection of 2/9 of the calculated initial daily insulin dose. Insulin lispro was injected 5 min prior to the test meal and regular human insulin was injected 30 min prior to the test meal. Plasma glucose, and serum insulin and C-peptide concentrations were determined before and at 1, 2, and 3 h after the meal. In addition, serum concentrations of insulin lispro were determined by a specific radioimmunoassay (19). This competitive radioimmunoassay has a lower limit of quantitation of <3 μU/ml and exhibits <0.05% cross-reactivity with human insulin, proinsulin, and C-peptide.

After the test meal, patients were instructed to administer either the insulin lispro or the regular insulin with an injection pen device (Becton Dickinson, Franklin Lakes, NJ), before each subsequent meal for a total of three times per day, and in the morning and in the evening all patients also received NPH insulin calculated according to the protocol published by Jovanovic et al. (14). Patients were instructed to perform self blood glucose monitoring (Accu-Check Advantage with memory; Roche Diagnostics, Indianapolis, IN) 0–30 min before and 1 h after the start of each meal. Hypoglycemia was defined as a blood glucose measurement of <55 mg/dl (3.1 mmol/l) or symptoms associated with hypoglycemia by the patient, or both. Frequency of hypoglycemic episodes was assessed at each weekly visit as recorded by the patient in her diary and as indicated by data from the glucose meter. HbA_{1c} and maternal insulin antibody concentrations were evaluated again at treatment week six, at delivery, and six weeks postpartum.

At each weekly visit, insulin dosage, diet, and exercise prescriptions were adjusted according to previously published protocols (14,20,21). Fetal well-being was monitored throughout the study with ultrasonography and fetal non-stress tests.

To determine if the absence of cord insulin lispro was attributable to lack of placental transfer or to undetectable insulin concentrations in the mothers, whose last meal-related injection of insulin lispro was many hours before the delivery, 10 women had insulin infused during labor and delivery. Insulin lispro or regular human insulin (depending on the treatment group) was infused intravenously during the active phase of the first stage of labor at a rate of 0.2 U · kg^{-1} · h^{-1} using an insulin infusion pump to achieve steady-state circulating insulin concentrations (1). Concomitant intravenous dextrose infusion at an initial rate of 2.55 mg · kg^{-1} · min^{-1} was administered and adjusted to maintain blood glucose concentrations between 70 and 90 mg/dl (3.9 and 5.0 mmol/l). Capillary glucose measurements were performed every 5 min until blood glucose stabilized and every 30 min thereafter.

Table 2—*Insulin antibody findings (median percent binding)*

	Insulin lispro–specific antibodies	Regular human insulin–specific antibodies	Cross-reactive antibodies	Total *n**
Reference range	(0–0.9)	(0–0.9)	(0–1.6)	
Baseline				
Regular human insulin	0.2 (0.1–0.375)	0.3 (0.1–0.4)	1.1 (0.9–1.375)	22
n_1	0	1	1	—
Insulin lispro	0.2 (0–0.3)	0.3 (0.15–0.45)	1.1 (0.8–1.25)	19
n_1	0	1	4	—
6 weeks after enrollment				
Regular human insulin	0.4 (0.225–0.6)	0.35 (0.1–0.5)	1.45 (1–1.85)	22
n_2	2	1	3	—
Insulin lispro	0.25 (0–0.45)	0.35 (0.125–0.5)	1.15 (1.025–1.7)	18
n_2	0	1	2	—
Maternal serum at delivery				
Regular human insulin	0.4 (0.075–0.6)	0.35 (0.175–0.5)	1.55 (0.9–2.025)	21
n_2	1	2	3	—
Insulin lispro	0.3 (0–0.5)	0.35 (0.075–0.425)	1.4 (1.075–2.325)	18
n_2	1	1	6	—
Umbilical cord blood				
Regular human insulin	0.3 (0–0.4)	0.3 (0.2–0.4)	1.1 (0.7–1.7)	21
n_1	0	0	3	—
Insulin lispro	0.1 (0–0.3)	0.4 (0.2–0.55)	1.1 (0.75–1.35)	18
n_1	0	1	2	—
Postpartum maternal serum				
Regular human insulin	0.3 (0.2–0.5)	0.1 (0.075–0.325)	1.7 (1.025–2.175)	21
n_2	0	1	4	—
Insulin lispro	0.25 (0.05–0.5)	0.25 (0–0.375)	1.6 (1.025–2.575)	18
n_2	1	0	4	—

Data are medians (interquartile range) for percent binding of radio-labeled material. n_1, number of values greater than reference range; n_2, number of values above reference range and two times baseline. *Numbers vary because of missing data.

At birth, cord blood samples were analyzed for serum insulin lispro, regular human insulin, and insulin antibody binding for all 41 women who were followed during their pregnancies. Neonates were weighed and Apgar scores (22), plasma glucose concentrations, complete blood counts, and bilirubin concentrations were determined. Heel stick glucose determinations were then performed at 2, 4, and 6 h after birth.

Statistical methods

Data were compared using standard two-tailed unpaired *t* tests, χ^2 tests, or Fisher's exact test, as appropriate. Areas under the curve for glucose, insulin, and C-peptide measured during the meal test were compared with *t* tests and also with multiple linear regression that controlled for potential confounders. For each woman, a percent of all preprandial readings in the hypoglycemic range and a percent of all postprandial readings in the hyperglycemic range were calculated and these percents were compared with *t* tests. Because the distribution of the percentage binding measurements was asymmetric and skewed to the right, these data are expressed as median values with the interquartile range (25th–75th percentile). A square root transformation was used to normalize these percentages before the analysis using a *t* test for each point in time.

RESULTS — A total of 42 patients participated in the standardized meal test and 41 of these were followed during pregnancy. Of the 42 patients, 23 were randomized into the regular human insulin group, and 19 into the insulin lispro group. Two women had a history of prior gestational diabetes, but neither had received insulin before. Those randomized to the insulin lispro group were older (34.2 years) than those in the regular human insulin group (29.8 years, $P < 0.01$), but there were no other significant differences between the groups (Table 1).

For most women, maternal insulin-specific antibodies, insulin lispro–specific antibodies, and cross-reactive antibodies were within the reference range at the time of enrollment. Two women had antibody binding to regular insulin and five, including one of the two with antibody to regular insulin, had cross-reactive antibodies (Table 2). At delivery, 14 women (6 regular and 8 lispro) had one of the antibodies out of range. With one exception, antibodies to regular and lispro insulin in the umbilical cord blood were all within the reference range, although five—three in the regular group and two in the lispro group—had cross-reactive antibodies that were out of range. When a change from baseline antibody response was evaluated for individual patients, no statistically significant differences were seen between the insulin lispro and regular human insulin groups. The highest single percentage antibody binding recorded during the study was in a woman who received regular human insulin, and at delivery her cross-reactive antibody binding was 10%. No insulin lispro was detected in umbilical cord blood, including the infants of the four women in the insulin lispro group who participated in the insulin infusion study during labor and delivery

Table 3—*Metabolic response to test meal*

	Time				Area under the curve	*P* value*	*P* value†
	Fasting	60 min	120 min	180 min			
Plasma glucose (mg/dl)							
Regular human insulin	81.5 ± 2.8	113.3 ± 4.1	99.6 ± 4.7	84.6 ± 5.0	51.5	0.025	0.031
Insulin lispro	79.8 ± 2.9	100.9 ± 4.5	86.8 ± 4.6	70.4 ± 3.6	23.4		
Serum insulin (μU/ml)							
Regular human insulin	17.0 ± 1.6	132.3 ± 9.3	62.1 ± 3.9	39.6 ± 3.2	171.7	0.025	0.019
Insulin lispro	14.4 ± 1.2	91.2 ± 10.7	62.3 ± 5.9	30.2 ± 2.0	132.6		
Serum C-peptide (ng/ml)							
Regular human insulin	1.8 ± 0.1	7.6 ± 0.2	5.5 ± 0.2	4.3 ± 0.2	10.5	<0.001	<0.001
Insulin lispro	2.1 ± 0.2	3.7 ± 0.1	3.4 ± 0.3	2.5 ± 0.3	3.0		
Serum insulin lispro (μU/ml)							
Insulin lispro	0‡	73.9 ± 10.0	56.30 ± 5.8	29.3 ± 2.8	—	—	—

Data are means ± SEM unless otherwise indicated. Glucose data were available for 42 women; insulin and C-peptide data were available for 41 women. **P* value from unpaired *t* test for comparison of area under the curve between regular and insulin lispro group; †*P* value from multiple linear regression controlling for age, BMI, and fasting glucose; ‡assay response below level of detection.

and who had insulin lispro concentrations of 1.7, 4.0, 4.9, and 5.2 μU, respectively.

During the test meal, patients treated with insulin lispro generally had lower plasma glucose, serum insulin, and serum C-peptide concentrations (Table 3). The areas under the curve for glucose, insulin, and C-peptide were lower for the insulin lispro group, a difference that remained significant when adjusted by multiple linear regression for age, BMI, and fasting plasma glucose concentration. Serum concentrations of insulin lispro were detectable during the 3-h test meal study.

Throughout the remainder of the pregnancy, the number of maternal hypoglycemic episodes, which were uncommon in both groups, were lower before breakfast in patients treated with insulin lispro (P = 0.025) but not before lunch or dinner (Table 4). The number of hyperglycemic episodes (serum glucose ≥120 mg/dl [6.7 mmol/l]) was also lower overall (P = 0.019) for patients treated with insulin lispro (Table 4), but there was little difference in occurrence of more severe hyperglycemia. Table 5 shows HbA_{1c} concentrations at enrollment and 6 weeks after insulin initiation. Although not significant, the insulin lispro group had somewhat higher HbA_{1c} at baseline. Because the reduction from baseline in the HbA_{1c} concentration was greater in the insulin lispro group, the two groups had similar concentrations by 6 weeks.

Maternal and fetal outcomes are presented in Table 6. There were no statistically significant differences between the groups in the proportion of cesarean deliveries, gestational age at delivery, or the neonatal parameters of height, weight, percentile rank, 1-min and 5-min Apgar scores. No newborn in either treatment group was macrosomic (>90th percentile), had intrauterine growth restriction or fetal abnormality, and none had neonatal hypoglycemia or hypocalcemia (data not shown).

CONCLUSIONS — In the Diabetes in Early Pregnancy Study, the prevalence of macrosomia in infants of diabetic mothers was 28.5% (3), and birth weight correlated positively with maternal postprandial blood glucose and HbA_{1c}. Combs et al. (8) also reported that macrosomia was associated with higher postprandial glucose concentrations. De Veciana et al. (9) described better fetal outcome with less neonatal

Table 4—*Maternal hypoglycemia before meals and hyperglycemia after meals*

Meal	Hypoglycemia (BG <55 mg/dl)	Hyperglycemia		
		BG ≥120 mg/dl	BG ≥130 mg/dl	BG ≥140 mg/dl
Breakfast				
Regular human insulin	0.93 ± 1.04*	7.3 ± 0.40	2.7 ± 0.48	0.6 ± 0.22
Insulin lispro	0.65 ± 0.13	5.5 ± 0.30	2.4 ± 0.63	0.6 ± 0.23
Lunch				
Regular human insulin	1.98 ± 0.81	6.8 ± 0.86	1.7 ± 0.41	1.0 ± 0.26
Insulin lispro	0.78 ± 0.37	4.5 ± 1.10	1.4 ± 0.38	1.0 ± 0.35
Evening meal				
Regular human insulin	1.43 ± 0.86	2.6 ± 0.54	1.0 ± 0.31	0.5 ± 0.18
Insulin lispro	1.26 ± 0.43	2.0 ± 0.51	0.9 ± 0.29	0.4 ± 0.10
Total				
Regular human insulin	2.20 ± 0.86	5.5 ± 0.47*	1.8 ± 0.30	0.69 ± 0.14
Insulin lispro	0.88 ± 0.25	4.0 ± 0.49	1.6 ± 0.34	0.65 ± 0.18

Data are means ± SEM for individual patient percentage of all blood glucose determinations in the hypo- or hyperglycemic range, derived from an aggregate of 25,000 capillary blood glucose determinations. BG, capillary blood glucose. *Statistically significant difference.

Table 5—*Maternal HbA_{1c} (%)*

	At enrollment	6 weeks later	Difference from baseline
Regular human insulin	5.24 ± 0.09	5.16 ± 0.12	0.07 (2.8%)
Insulin lispro	5.47 ± 0.09	5.12 ± 0.11	0.35 (5.7%)
P value	0.0801	0.7508	0.0018

Data are means ± SEM.

hypoglycemia, macrosomia, and cesarean delivery in women whose gestational diabetes was managed by control of the 1-h postprandial glucose concentrations than in those managed by preprandial glucose concentrations.

Previous reports have documented antibodies to insulin in gestational diabetic women even if they have never received insulin (23). In this study, two women had regular insulin antibodies at baseline and an additional four had cross-reactive antibodies. Whether these women will develop type 1 diabetes remains to be seen. The duration of action of insulin lispro is shorter than regular human insulin because of its rapid absorption (12), which may also decrease its immunogenicity. The literature supports this theory. Patients without previous exposure to exogenous insulin who are treated with animal insulin may experience increases in antibody binding up to 15% after as little as two months of therapy (24). Regular human insulin is associated with less antibody response than is animal insulin, and the antibody response associated with insulin lispro is no higher than with regular human insulin (17,18,25). In the present study no greater increase in lispro-specific or insulin-specific antibodies was demonstrated in the insulin lispro group than in the regular human insulin group, although some women had an antibody response similar to the previous published reports in nonpregnant diabetic subjects (17,18,25,26).

Because placental transfer of insulin occurs when complexed with immunoglobulin, the lack of insulin lispro–induced antibody formation could be expected to result in little, if any, placental transfer of insulin lispro to the neonate (10,17,18,25). During parturition, the subset of mothers who received a continuous infusion of insulin lispro had measurable concentrations of insulin lispro but no insulin lispro could be detected in the cord blood. These findings lend support to the conclusion that insulin lispro does not cross the placenta.

The rapid absorption of insulin lispro from the subcutaneous site allows for a faster peak insulin concentration than is found with regular human insulin (27), which more closely mimics the physiologic first-phase insulin release and results in lower postprandial glucose concentrations (12). This finding may make insulin lispro a valuable therapeutic option in the treatment of gestational diabetes and prevention of neonatal complications. In addition, insulin lispro upregulates insulin receptors (28,29). In the present study, the postprandial glucose rise in response to the test meal was significantly less after a standardized dose of insulin lispro than after regular human insulin. In addition to lower postprandial glucose concentrations in response to the test meal, insulin lispro was effective in lowering overall glycemia, as documented by an improvement in HbA_{1c} after only six weeks of therapy. Thus, insulin lispro may be a valuable therapeutic option in the treatment of gestational diabetes. In this study, however, the patients and their physicians were not blinded to their treatment. Therefore, these results need to be evaluated with caution.

Clinical significance for the fetus may be difficult to extrapolate from these findings as well. Fetal malformation and spontaneous abortion rates are high when HbA_{1c} concentrations are >4 SDs above the mean of a normal population (30–33), but most women with gestational diabetes have lower levels of glycemia and do not experience hyperglycemia during organogenesis. Thus, the rationale for normoglycemia in gestational diabetes is to prevent macrosomia. This study also showed a clinical benefit for the mother because, despite the improved glycemic control, the women in the lispro group actually had less hypoglycemia.

In conclusion, insulin lispro proved to be safe with an antibody formation comparable to regular human insulin. Thus, whether macrosomia is linked to postprandial hyperglycemia or maternal insulin antibody formation, for patients with gestational diabetes, insulin lispro demonstrated treatment benefits comparable to those of regular human insulin.

Table 6—*Maternal and fetal outcomes*

	Insulin lispro group	Regular human insulin group
n	19	22*
Cesarean section delivery	7 (36.8)	6 (27.3)
Gestational week at delivery	38.8 ± 0.3	38.8 ± 0.2
Neonatal parameters		
Length (cm)	49.8 ± 0.5	49.5 ± 0.3
Weight (g)	3,098 ± 202	3,169 ± 78
Percentile rank†		
10–25	6	6
25–50	6	8
50–75	4	6
75–90	3	2
Apgar score (1 min)	8.3 ± 0.2	7.5 ± 0.4
Apgar score (5 min)	9.0 ± 0	8.7 ± 0.2

Data are *n*, *n* (%), or means ± SEM. *One woman participated in the meal test only; †specific for sex, gestational age, and ethnicity. No differences were statistically significant.

Acknowledgments— This research was funded in part by a research grant from Eli Lilly and Company, Indianapolis, IN. L.J., S.I., D.J.P., K.H., and M.G. have received research support from the Sansum Medical Research Institute.

The authors wish to express appreciation to Kenneth E. Robertson, Renee Lynch, Anthony Zagar, and Sheng Loh, MD, for technical assistance and to Peggy Campbell for editorial assistance in the preparation of the manuscript.

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