

Comparison of Human Regular and Lispro Insulins After Interruption of Continuous Subcutaneous Insulin Infusion and in the Treatment of Acutely Decompensated IDDM

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OBJECTIVE — To compare the rapidity of metabolic decompensation after interruption of CSII between human regular and lispro insulin and to compare these two insulins in the correction of the hyperglycemia and ketosis of mildly decompensated IDDM. Lispro insulin may be especially useful for insulin pump therapy (continuous subcutaneous insulin infusion [CSII]).

RESEARCH DESIGN AND METHODS — A total of 18 patients with well-controlled IDDM (HbA_{1c} $7.7 \pm 1.1\%$, age 30 ± 11 years) were studied. All were being treated with CSII (nine with human regular and nine with lispro insulin). The study consisted of two phases: 1) an insulin interruption phase, in which the basal insulin infusion was stopped (at 0300) and plasma insulin, glucose, and β -O-hydroxybutyrate (β -OHB) were measured every 15–60 min for 6 h after interruption of the insulin infusion and 2) an insulin replacement phase, which involved measuring plasma insulin, glucose, and β -OHB for 2 h after a single injection of either human regular or lispro insulin to correct the hyperglycemia and ketosis that developed during the first phase of the study.

RESULTS — After interruption of the basal insulin infusion during the insulin interruption phase, plasma insulin levels fell gradually in both groups to nadir values of 1.6 ± 0.8 and 2.0 ± 1.2 μ U/ml in the regular insulin- and insulin lispro-treated groups, respectively. Plasma glucose concentrations rose to 13.8 ± 1.9 and 16.0 ± 1.7 mmol/l in the regular insulin- and insulin lispro-treated groups, respectively. No significant differences were seen between the therapy groups at any time in the insulin levels or in the concentrations of plasma glucose or β -OHB. In the insulin replacement phase, insulin levels rose more rapidly in those treated with lispro insulin, reaching a greater peak value (e.g., at 60 min, plasma insulin 25 ± 3.4 vs. 15.6 ± 2.6 μ U/ml, $P < 0.05$). In association with this, plasma glucose decreased to a lower nadir after lispro insulin (9.7 ± 0.4 vs. 13.7 ± 0.7 mmol/l, lispro- vs. regular-treated groups at 120 min after insulin administration, $P < 0.01$). β -OHB levels decreased rapidly in both groups.

CONCLUSIONS — In patients treated with CSII, interruption of the basal insulin infusion in the middle of the night does not result in more rapid metabolic decompensation in patients treated with lispro compared with those treated with regular human insulin. Lispro insulin is effective in treating mild ketosis and hyperglycemia, and its rapid action may be advantageous in the “sick day” management at home of patients with IDDM.

Lispro insulin is an analog of human insulin in which the amino acids at positions 28 and 29 on the B-chain are reversed in sequence. This change does not alter the metabolic action of insulin but results in a faster rate of absorption from injection sites than does regular human insulin (1,2). Pharmacokinetic studies indicate that lispro insulin acts within 15 min, peaks in 1 h, and disappears within 2–4 h after subcutaneous injection (3). The rapid onset and short duration of lispro insulin suggest that the analog may be especially useful in insulin pump therapy (continuous subcutaneous insulin infusion [CSII]) (4).

CSII is a means to clinically mimic the physiology of normal insulin secretion and has been used successfully in intensively treated patients with IDDM. However, interruption of insulin infusion because of catheter occlusion or other causes is a concern when using CSII, particularly at night, because it can lead to metabolic decompensation and diabetic ketoacidosis. Because lispro insulin is more rapidly absorbed from the subcutaneous injection site, patients using lispro as their pump insulin may be at greater risk for more rapid metabolic decompensation in the case of interruption of the insulin infusion (5). This study was undertaken to compare the rapidity of metabolic decompensation after interruption of CSII between buffered human regular insulin and lispro insulin.

Acute hyperglycemia and ketosis are common occurrences in patients with IDDM, regardless of the type of treatment, and are usually the result of an intercurrent illness. Such “sick days” are normally managed at home by subcutaneous injections of human regular insulin in doses of 0.2 U/kg every 2–4 h. A second aim of this study, therefore, was to determine whether the more rapid absorption of lispro insulin might provide more rapid correction of hyperglycemia and mild ketosis in IDDM.

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Abbreviations: β -OHB, β -O-hydroxybutyrate; CSII, continuous subcutaneous insulin infusion.

Table 1—Clinical characteristics of study subjects

	Human regular insulin	Insulin lispro
<i>n</i>	9	9
Weight (kg)	71 ± 5	78 ± 4
M/W	5/4	4/5
Age (years)	30 ± 4	31 ± 3
Duration of IDDM (years)	16 ± 2	15 ± 2
HbA _{1c} (%)	7.6 ± 0.4	7.8 ± 0.4
Total daily insulin dose (U · kg ⁻¹ · day ⁻¹)	0.6 ± 0.1	0.7 ± 0.1
Basal (% total daily insulin dose)	50 ± 3	56 ± 3

Demographic data are means ± SD; other data are means ± SEM. For HbA_{1c}, the nondiabetic range is <6.0%.

RESEARCH DESIGN AND METHODS

Subjects

Eighteen patients with IDDM (10 men, 8 women) were studied. All were being treated with CSII; nine were treated with buffered human regular insulin (Velosulin, Novo Nordisk, Princeton, NJ) and nine with lispro insulin (Humalog, Eli Lilly, Indianapolis, IN). Insulin lispro is buffered with dibasic sodium phosphate. None of the patients had evidence of impaired renal function, macrovascular complications of IDDM, or other chronic disease. The clinical characteristics of the subjects are summarized in Table 1. The protocol was approved by the Yale Human Investigation Committee, and each subject gave written informed consent to the study.

Protocol

The protocol consisted of two phases. The first phase (insulin interruption phase) involved an 8-h period of acute insulin withdrawal as a result of discontinuation of CSII at 0300. To be eligible for this phase of the study, plasma glucose levels had to be between 3.3 and 8.3 mmol/l (60–150 mg/dl) during the 1 h before interruption of the basal insulin infusion (6). The second phase (insulin replacement phase) involved studying the same subjects after a single subcutaneous injection of either human regular (Humulin, Eli Lilly) or lispro insulin given to correct the hyperglycemia and ketosis that developed during the first phase. To be eligible for this phase of the study, the patients had to have developed moderate hyperglycemia (plasma glucose >13.9 mmol/l [250 mg/dl]) or moderate ketonuria during the insulin interruption phase.

All subjects were admitted to the Yale General Clinical Research Center in the afternoon of the first day of the study. An

intravenous catheter was inserted into an antecubital vein for blood sampling. Subjects received their usual basal rates and presupper (at ~1730) and bedtime (2200) bolus doses in order to achieve a plasma glucose of 3.3–8.3 mmol/l (60–150 mg/dl) before the interruption of CSII at 0300. In two subjects, plasma glucose levels were >8.3 mmol/l between 0200 and 0300, and they were discharged and readmitted on a second occasion when target glucose levels were achieved before initiation of the first phase of the study. Baseline insulin and substrate concentrations were obtained between 0230 and 0300, and then the CSII basal insulin infusion was stopped. Blood samples for the measurement of glucose were obtained every 15 min, for insulin every 10–30 min, and for β-O-hydroxybutyrate (β-OHB), bicarbonate, and pH every 1 h. In addition, urinary ketone measurements were obtained with every void. The insulin interruption phase of the study was terminated after 8 h or earlier if plasma glucose was >19.4 mmol/l (350 mg/dl) or if there was moderate ketonuria.

After the period of insulin withdrawal, the patients were randomly assigned to receive a single injection of either regular or lispro insulin (0.2 U/kg body wt), irrespective of the insulin they had been receiving by CSII. The insulin was given into the subcutaneous tissue of the anterior abdominal wall. After this, blood sampling was continued for an additional 2 h.

Measurements and analysis

Plasma glucose levels were measured by the glucose oxidase method with a Beckman glucose analyzer (Brea, CA). Plasma free insulin was measured by double antibody radioimmunoassay (Diagnostic Systems Laboratories, Webster, TX). Plasma samples were treated with polyethylene glycol immediately after separation to precipi-

tate antibody-bound insulin, and the supernatant was measured for free insulin. Serum β-OHB was measured using an enzymatic assay as described previously (7).

Demographic data (Table 1) are expressed as means ± SD and other data as means ± SEM. Changes in glucose, insulin, and β-OHB were compared between groups using Student's *t* tests and analysis of variance with repeated measures design.

RESULTS

Insulin interruption phase

Of the nine patients who received lispro insulin, two completed the 480-min insulin interruption phase, but in the remaining seven, the study was shortened: ketonuria developed in three subjects, and plasma glucose rose above 19.4 mmol/l (350 mg/dl) in four subjects. Similarly, in the nine patients treated with regular insulin, three completed 480 min, and in six subjects, the study was shortened (three with moderate ketonuria and three with glucose above 19.4 mmol/l [350 mg/dl]). The duration of the insulin interruption phase of the study ranged from 240 to 480 min in both groups, and the mean duration did not differ significantly between the two groups (400 ± 26 vs. 377 ± 25 min, regular vs. lispro, NS).

Figure 1 shows insulin, glucose, and β-OHB profiles after interruption of CSII in patients receiving regular and lispro insulin for the first 6 h of the study. Baseline plasma insulin concentrations during basal insulin infusion (CSII) were similar in the regular (8.7 ± 1.9 μU/ml) and lispro (11.8 ± 3.1 μU/ml) treatment groups. After interruption of basal infusion, insulin levels gradually decreased to a nadir value of 1.6 ± 0.8 μU/ml in the regular insulin group and 2.0 ± 1.2 μU/ml in the lispro insulin group. The insulin values did not differ significantly between the groups at any time point.

Plasma glucose values were also similar in the two groups before interruption of insulin administration (5.3 ± 0.5 vs. 5.9 ± 0.8 mmol/l, lispro vs. regular, respectively), and no substantial changes were noted for the 1st h. Over the subsequent 5 h, glucose values substantially increased in both groups, and the magnitude of the increase in plasma glucose did not differ between the treatment groups.

Serum β-OHB concentrations are shown in Fig. 1. β-OHB values increased in both groups during the period of insulin withdrawal and were similar at each time point. Peak β-OHB values were similar

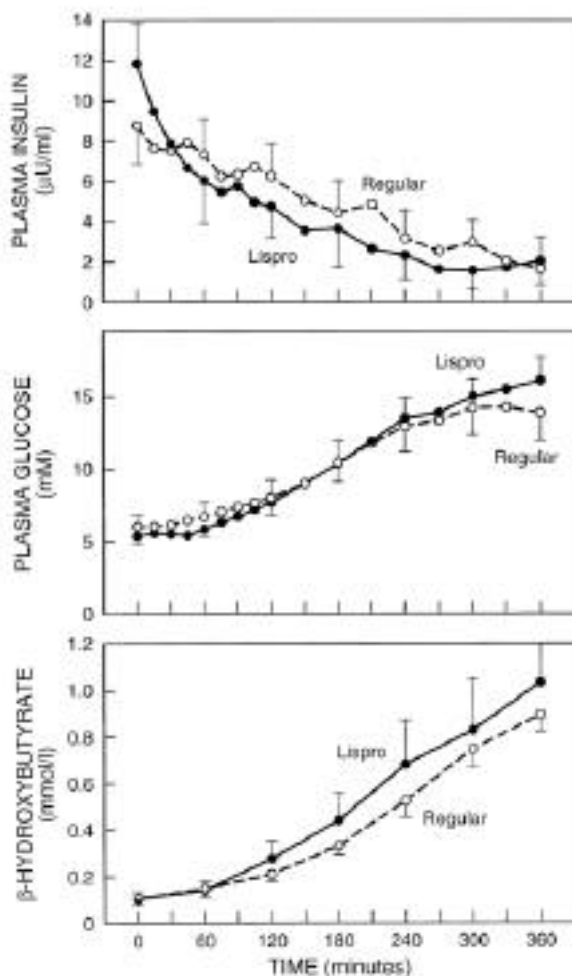


Figure 1—Changes in plasma insulin, plasma glucose, and serum β -OHB concentrations after cessation of basal insulin infusion (time 0) in patients treated with lispro or regular human insulin.

between groups (0.89 ± 0.072 vs. 1.02 ± 0.22 mmol/l, regular vs. lispro insulin).

No subjects became acidotic or showed evidence of dehydration during the study, and serum electrolytes remained within the reference range (data not shown).

Insulin replacement phase

A total of 17 subjects completed the second phase of the study: one subject was excluded because plasma glucose and urine ketone values did not increase sufficiently to qualify in this phase of the study. All the remaining subjects exhibited moderate or large ketonuria as well as a plasma glucose >13.9 mmol/l (250 mg/dl) at the commencement of this phase. As shown in Table 2, baseline insulin, glucose, and β -OHB levels did not differ significantly between the patients randomized to receive a subcutaneous injection of regular or lispro insulin. As shown in Fig. 2, insulin

levels became significantly different 30 min after insulin administration in subjects who received lispro compared with regular insulin (plasma insulin: 24 ± 5.6 vs. 13 ± 2.6 μ U/ml, lispro vs. regular insulin, $P < 0.05$). In association with the more rapid increase in plasma insulin, plasma glucose levels became significantly lower in the lispro insulin group than in the regular insulin group by 40 min after the insulin was administered. At 120 min, plasma glu-

cose had decreased to 9.7 ± 0.4 vs. 13.7 ± 0.7 mmol/l in those given lispro vs. regular insulin ($P < 0.01$). β -OHB concentrations decreased rapidly in both groups (Fig. 2), and there was no significant difference in values between those given regular and those given lispro insulin.

CONCLUSIONS—The primary aim of this study was to determine whether the use of lispro compared with human regular insulin in CSII places patients at increased risk for more rapid metabolic decompensation in the event of interruption of the insulin infusion. This is an important question, because several recent studies indicate that the pharmacokinetic properties of lispro insulin make it well suited for CSII. Because of a more rapid absorption of premeal bolus doses of lispro versus regular insulin, better control of postprandial hyperglycemia can be achieved without increasing the rate of hypoglycemia (8–10). However, the more rapid disappearance of lispro from its subcutaneous injection site might also make lispro-treated patients more at risk for diabetic ketoacidosis because of catheter occlusion or other causes of disruption of the insulin infusion. Thus, it is particularly noteworthy in this study that interruption of the basal insulin infusion resulted in no difference between the treatment groups with respect to the rise in plasma glucose or serum ketone levels. It is also reassuring that lispro has been found to be stable in insulin infusion systems (11) and that in short-term randomized clinical trials, the frequency of catheter occlusion and other site-related problems was not increased with lispro compared with buffered human regular insulin (4).

In CSII-treated patients, interruptions of the insulin infusion are especially problematic when they occur at night, because patients can be deprived of insulin for many hours while asleep without realizing that a system malfunction has occurred. We chose to interrupt the insulin infusion at 0300, at least 5 h after the last premeal bolus dose of

Table 2—Plasma insulin, glucose, and serum β -OHB at the commencement of the insulin replacement phase

	Human regular insulin	Insulin lispro	P values
Plasma insulin (μ U/ml)	0.9 ± 0.5	1.8 ± 1.0	0.61
Plasma glucose (mmol/l)	18.9 ± 0.9	17.5 ± 0.8	0.51
β -OHB (mmol/l)	1.01 ± 0.14	1.32 ± 0.16	0.59

No significant differences were noted between the groups at this time.

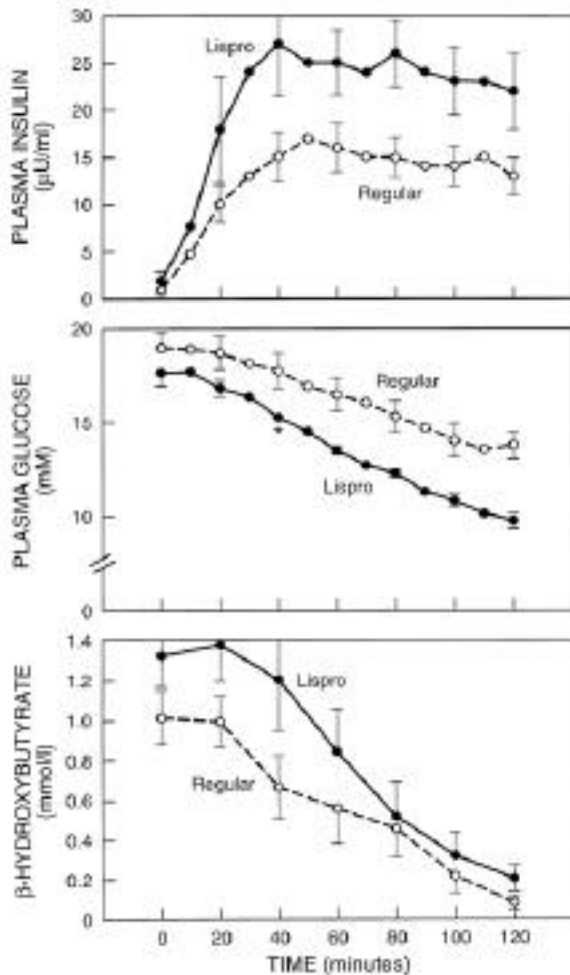


Figure 2—Changes in plasma insulin, plasma glucose, and serum β-OHB concentrations after a single subcutaneous injection (0.2 U/kg) of either lispro or regular human insulin. Insulin concentrations in the lispro-treated group were greater by 30 min ($P < 0.01$), and plasma glucose values were lower by 40 min ($P < 0.01$).

insulin, to simulate conditions that a patient with IDDM might experience. Consequently, plasma insulin levels were relatively low in both groups before the insulin infusion was interrupted, and the further decrease in plasma insulin concentrations was similar when the basal infusion was stopped. It remains to be determined, however, whether the response to a pump malfunction might differ between lispro and regular insulin users if it occurs during waking hours, such as after a large premeal bolus dose of insulin.

At the end of the first phase of the study, all but one of the patients were hyperglycemic and ketotic. This provided a unique opportunity to examine a second question under carefully controlled conditions: are there advantages of insulin lispro over human regular insulin in the treatment of acutely decompensated diabetes?

To address this issue, patients were randomly assigned to receive a subcutaneous injection of 0.2 U/kg body wt (~10–15 U) of either lispro or regular insulin after completion of the first phase of the study, irrespective of the type of insulin they were using with CSII. As expected, insulin levels rose more quickly and to a higher plateau after subcutaneous injections of lispro compared with regular insulin. Consequently, the fall in plasma glucose was greater in the group treated with insulin lispro. This finding is consistent with that of Holleman et al. (12), who studied 27 patients with IDDM who were hyperglycemic but not ketotic. In our study, pretreatment β-OHB levels were only modestly elevated, and the decrease in these concentrations was similar in both treatment groups. It is likely, but currently unproven, that the more rapid absorption of lispro would also be more effective than reg-

ular insulin in correcting the more severe ketosis that develops during intercurrent illnesses in patients with IDDM. Nevertheless, since plasma glucose fell more quickly and serum ketones were fully suppressed with lispro, the current observations support the contention that lispro insulin may be more effective than regular insulin in the “sick day” management at home of patients with IDDM.

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