Insulin lispro reduced nocturnal hypoglycemic episodes in type 1 diabetes mellitus when used to achieve tight glycemic control

Heller SR, Amiel SA, Mansell P, on behalf of the U.K. Lispro Study Group. **Effect of the fast-acting insulin analog lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy.** Diabetes Care. 1999 Oct;22:1607-11.

QUESTION

In patients with type 1 diabetes mellitus who are using intensive insulin therapy to achieve tight glycemic control, is insulin lispro as effective as human regular insulin in reducing hypoglycemic episodes?

DESIGN

Randomized {allocation concealed*}†, unblinded,* crossover trial with planned follow-up at 4 and 8 months.

SETTING

11 diabetes outpatient clinics in the United Kingdom.

PATIENTS

135 patients (mean age 38 y, 53% men) who had had type 1 diabetes for ≥ 2 years, used a basal bolus regimen for ≥ 3 months, had a hemoglobin (Hb) A_{1c} level < 8%, and expressed a desire to achieve tight glucose control. Exclusion criteria were proliferative retinopathy, symptomatic peripheral neuropathy, serum creatinine level > 250 µmol/L, or > 3 hospital admissions for severe hypoglycemia in the previous 12 months. Follow-up was 100% at 4 months.

INTERVENTION

After a 2-month run-in period, patients were allocated to receive a basal bolus regimen of insulin lispro for 4 months and then human regular insulin for an additional 4 months (n = 68) or human regular insulin for 4 months and then insulin lispro for an additional 4 months (n = 67). Patients were instructed to inject insulin lispro immediately before a meal and to inject human regular insulin about 30 minutes before a meal. All patients used human neutral protamine Hagendorn (NPH) insulin at night. Data gathered during only the first 4 months were analyzed because the order of the intervention affected the results independently of the intervention.

MAIN OUTCOME MEASURES

Number and severity of hypoglycemic episodes and HbA_{1c} level.

MAIN RESULTS

At 4 months, no difference existed in HbA_{1c} levels between those who received insulin lispro (HbA_{1c} 6.0%) and those who received human regular insulin (HbA_{1c} 6.2%). Insulin lispro was associated with fewer hypoglycemic episodes (775 vs 1156, P = 0.04) and, specifically, with fewer nocturnal hypoglycemic episodes (52 vs 181, P = 0.001) than was human regular insulin.

CONCLUSION

Insulin lispro was as effective as human regular insulin in achieving glycemic control and was associated with fewer total and nocturnal hypoglycemic episodes in patients with type 1 diabetes mellitus who were using intensive insulin therapy.

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*See Glossary.

†Information provided by author.

COMMENTARY

Tight control of blood glucose levels reduces the incidence of microvascular events in type 1 diabetes 50% more than does conventional therapy (1) but substantially increases the risk for hypoglycemia (2). Exposure to frequent mild hypoglycemia can induce hypoglycemic unawareness, which, in turn, can increase the risk for severe hypoglycemia occurring without warning symptoms.

Insulin lispro is a rapid-acting insulin analogue, with onset of action within 15 minutes of injection, a peak at 30 to 90 minutes, and a duration of 3 to 5 hours. This profile mimics the normal postprandial insulin response of a person without diabetes far more closely than does injection of regular insulin, which peaks 2 to 4 hours after injection and lasts up to 8 hours.

The study by Heller and colleagues confirms the earlier findings of a similar study by Holleman and colleagues (3) that insulin lispro causes less hypoglycemia, especially at night, than does regular insulin in patients with type 1 diabetes who have near-normal glucose levels. Both studies used a randomized crossover design in which patients received basal bolus insulin therapy, using either preprandial insulin lispro for several months followed by regular insulin for a similar period of time or vice versa. In the study by Heller and colleagues, a period effect occurred where patients who were initially allocated to insulin lispro continued to have a lower incidence of hypoglycemia even after being switched to regular insulin. Such a period effect did not occur in the Holleman study. The only observed difference between the study populations in the Holleman study and this study was the shorter duration of diabetes in the latter study (16 vs 13 y). Taken together, these studies support the use of insulin lispro in patients with type 1 diabetes to optimize glycemic control while minimizing hypoglycemia.

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