

Benefits of lispro insulin

Control of postprandial glucose levels is within reach

This is the second of three articles on insulin therapy

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Preview: How well would the following fit into your schedule? You must know when you will eat throughout the day, and about an hour beforehand you must inject an appropriate amount of insulin to offset the amount of carbohydrate you intend to consume. For many diabetic patients who use regular insulin, these are the requirements. Dr Bohannon describes a newly approved insulin that goes into action and gets out of the body faster, more closely mimicking the body's natural insulin response to food.

Controlling diabetes to a near-normoglycemic state decreases the microvascular complications, including nephropathy, neuropathy, and retinopathy, in both type I and type II disease (1,2). However, achieving the goal of strict glycemic control has been hampered by the unphysiologic time course of exogenous insulin preparations (3). Use of intensive insulin regimens to improve glucose control has resulted in a threefold increase in the incidence of significant hypoglycemia in the Diabetes Control and Complications Trial (1,2)

Maintaining normoglycemia after meals has been especially difficult. Soluble regular insulin preparations usually take 2 to 4 hours to reach a peak blood level (4). Thus, the insulin level peaks a considerable time after meal carbohydrate has been absorbed, leading to a postprandial glucose peak followed by a relatively sluggish (occurring over 3 to 6 hours) return of blood glucose to the preprandial level. The glucose-lowering effect of regular insulin may continue 6 to 8 hours after an injection, sometimes causing late postprandial hypoglycemia before the next meal.

Various strategies have been used to try to decrease postprandial hyperglycemia and avoid late postprandial hypoglycemia. In Europe, one method has been to use acarbose (Precose) or another alpha-glucosidase inhibitor to slow digestion of carbohydrate. In the United States, a common approach, used most often in children and pregnant patients, has been to divide daily food intake into six small meals spaced about 3 hours apart.

With the advent of the new synthetic insulin lispro (Humalog), control of postprandial blood glucose levels may be easier to achieve.

Properties and effects

Lispro (pronounced "lice-pro") insulin takes its name from the 28th and 29th amino acids on the insulin B chain, lysine and proline. (Midway through global clinical trials, when worldwide release of the insulin was being anticipated, the spelling was changed from lyspro to lispro because some languages do not contain the letter y.) Lispro insulin has the same amino acid composition and isoelectric properties as human insulin, but in lispro, lysine (B28) and proline (B29) are reversed from their normal order. This reversal affects how the insulin molecules interact with one another.

Lispro solution is made up of, in part, 100 U/mL of lispro, zinc oxide, phenolic preservatives, glycerin, and water. Molecules of lispro insulin have less propensity for self-association than do those of human insulin. Therefore, when lispro insulin is injected into subcutaneous tissue, the phenolic compounds dissipate virtually immediately, leaving unstable zinc complexes that quickly dissociate into their monomeric subunits. The result is a subcutaneous absorption rate equivalent to what would be found in a truly monomeric insulin, which is at least twice as fast-acting as regular human insulin (5).

Lispro insulin has been studied extensively in worldwide clinical trials of more than 3,000 patients. Compared with regular human insulin, it has not been found to cause an increase in insulin antibody production (6), incidence of death or serious or unexpected adverse events, or severe hypoglycemia. It is compatible with

and may be mixed with NPH or ultralente insulin in the same syringe without any change in its onset, peak, or duration of action if given immediately. It has also been used in insulin pumps (7,8).

Clinical advantages over regular insulin

The glucose-lowering effects of regular human insulin and lispro insulin administered intravenously are identical. However, when injected subcutaneously, lispro insulin achieves peak absorption in only 1 hour, and its duration of action is only 4 hours (compared with 6 to 8 hours for regular human insulin) (9).

Another advantage of lispro insulin is decreased intraindividual and interindividual variability in insulin absorption (10). With regular insulin, some patients have reasonable postprandial glucose control from an injection given 15 or 20 minutes before a meal, but others require an injection 60 to 90 minutes before a meal. With lispro, this variability is greatly decreased. Lispro insulin can be administered virtually immediately (0 to 15 minutes) before a meal and can achieve postprandial glucose control that is as good as or better than that of regular insulin injected 30 to 60 minutes before a meal (which is the recommended timing). This effect is true of insulin-pump administration as well as subcutaneous injection. (However, the much shorter duration of action of lispro insulin may allow rapid onset of diabetic ketoacidosis in patients with type I diabetes if insulin infusion is interrupted, such as by pump malfunction or tube leakage.)

As would be expected from its more rapid onset and peak action, lispro insulin significantly reduces 1- and 2-hour postprandial glucose-level excursions (in patients with either type I or type II diabetes) (11-13). Surprisingly, initial studies found relatively little effect on hemoglobin A1c levels. Researchers suggested that this finding may be due to the somewhat more optimized administration of regular human insulin during the clinical trials, since subjects were strongly directed to take their regular insulin 30 to 60 minutes before meals.

Unfortunately, in free-living outpatients not involved in clinical studies, correct timing of

regular-insulin doses is not usually adhered to this closely. Part of the reason for this may be that physicians do not educate patients about or adequately emphasize the importance of insulin dosing in relation to meals. Patients should be taught and periodically reminded that if they are using regular insulin, they should administer it 30 to 60 minutes before meals to achieve acceptable postprandial glucose control. It will be interesting to see the effects on hemoglobin A1c levels among outpatients when lispro insulin has been available for several months.

Because of its shorter duration of action, lispro insulin results in less late postprandial hypoglycemia than regular human insulin (14-16). The 4- to 8-hour "tail" of action found with regular human insulin is not present with lispro insulin, so the likelihood of late hypoglycemia is reduced. This advantage is especially apparent at night in patients with tight glucose control (hemoglobin A1c < 7%) (17,18). The shorter duration of action of lispro insulin will be greatly welcomed by patients who live in fear of nocturnal hypoglycemia (19), some of whom intentionally administer inadequate insulin doses to lessen the risk, preferring instead to accept a high fasting blood glucose level.

Timing considerations

Because of its short duration of action, lispro insulin used alone must be administered subcutaneously every 4 to 6 hours in patients with type I diabetes to prevent insulin lack, hyperglycemia, and ketoacidosis. For this reason, long-acting or basal insulin should be used at night to control the fasting blood glucose level and during the day if lispro injections are separated by more than 5 hours.

Late dinner eaters and snackers

During trials, many investigators recommended concurrent use of NPH and lispro insulin at breakfast to control the prelunch blood glucose level when the period between breakfast and lunch was 5 hours or more. In San Francisco, we found that most of our subjects ate lunch within about 4 hours of breakfast, so they had no problem with prelunch hyperglycemia owing to loss of lispro activity. However, their usual

pattern was to have lunch about noon and dinner between 7 and 8 pm, which led to predinner hyperglycemia due to waning of lispro action. Thus, we found it most appropriate to administer NPH insulin with lunch in these subjects to control the predinner blood glucose level. Usually, only a small dose (eg, 2 to 5 U) was required, since the NPH insulin was not needed to control a postprandial blood glucose level, but rather to merely meet the basal insulin requirement between meals.

In subjects who routinely have a midafternoon snack, another dose of lispro may be given midafternoon instead of or in addition to the NPH dose at lunch. Lispro insulin is administered to control postprandial glucose levels, so when the snack contains a significant amount (>5 to 10 g) of carbohydrate, a lispro injection must be given with it. We found administration of lispro by a pen injection device to be very convenient in this situation. Insulin cartridges used in pen injection devices have been available in the United States for many years. Available forms are regular (Novolin R PenFill, Humulin regular), NPH (Novolin N PenFill, Humulin NPH), and 70/30 forms (Novolin 70/30 PenFill, Humulin 70/30). As of this writing, release of cartridges of lispro insulin is expected by January 1997.

Slow eaters and "grazers"

In phase III clinical studies, more than 75% of subjects preferred lispro insulin. Subjects who preferred regular human insulin included those who ate very slowly at all meals and those who consumed their daily intake by "grazing" (ie, having small amounts of carbohydrate throughout the day rather than large amounts in two or three meals).

One subject, who liked to dawdle over meals for an hour or more, found that he routinely became hypoglycemic midway into meals. People who had achieved good overall (including postprandial) control of blood glucose levels by grazing throughout the day found that they needed to eat a larger amount of carbohydrate shortly after a lispro injection to prevent hypoglycemia. They could not continue to snack without taking another lispro injection

or they would have hyperglycemia before the next "meal" injection was due.

Children with unpredictable eating habits

A potential advantage of lispro insulin is the peace of mind it may bring to parents of children who are fussy eaters. Many parents worry when they give regular insulin to their child before a meal and then the child decides that he or she is not hungry or does not like what is being served. The parents realize that the child has consumed an inadequate amount of carbohydrate to engage the insulin, so they frantically offer juice or sweets to prevent hypoglycemia. This pattern not only results in poor nutrition, but rewards poor eating habits.

Alternatively, some parents inject regular human insulin after they see how much their child has eaten. Although they know that this method results in significant postprandial hyperglycemia, they have chosen to accept the consequences rather than live in fear of hypoglycemia and possible convulsions (20).

With the advent of lispro insulin, an injection given immediately after meals is far less likely to cause significant prolonged hyperglycemia. It may also decrease late postprandial hyperglycemia (21).

Dieters and erratic eaters

An advantage of lispro insulin that was noted by many subjects (especially women) was that as long as they had taken some long-acting insulin to maintain a basal level, they could skip a meal if they were dieting or not hungry. With proper dosing of long-acting insulin, the lispro dose could be skipped or decreased according to meal size. Subjects found that carbohydrate counting permitted the most flexibility in dosing and thus in lifestyle by allowing varying-sized meals (measured by carbohydrate amount) to be consumed at various times of the day and night. Active subjects with erratic daily schedules especially appreciated this flexibility.

Type II diabetics

Insulin-treated type II diabetics receiving regular and NPH insulin would probably benefit from substituting lispro for the regular insulin

(22). Even in patients willing to administer only prebreakfast and predinner injections, lispro insulin would decrease postprandial glycemia after those two meals, and NPH insulin in the same syringe would have an effect similar to what it had when previously mixed with regular insulin. When regular and NPH insulin are used together before breakfast, the "tail" of regular insulin (lasting from 4 up to 8 hours after injection) provides some coverage of lunch in addition to that provided by the NPH insulin. Therefore, a slightly higher dose of NPH mixed with lispro insulin might be required to adequately insulinize the patient for lunch when the injection is given before breakfast, and slightly less lispro insulin (compared with regular insulin) might be necessary to control the postprandial glucose level.

Exercisers

Use of lispro insulin also simplifies exercise in patients with diabetes. With use of regular human insulin, unanticipated exercise performed 3 to 4 hours after an injection often results in hypoglycemia unless adequate carbohydrate is consumed to avoid it. With lispro insulin, most of the glucose-lowering effect is gone by 2 to 2 1/2 hours after an injection, and the small amount of residual insulin usually maintains the glucose level without actively decreasing it. Thus, exercising 3 to 4 hours after an injection of lispro insulin is less likely to cause hypoglycemia than is exercising after use of regular insulin (23). However, exercising 5 or more hours after a lispro injection, in the absence of basal insulin administration, is likely to increase the blood glucose level (because exercise induces glucose-raising counterregulatory responses in the absence of adequate insulinization).

Price considerations

Prices of insulin vary in different regions across the country according to managed care formularies, contractual bidding arrangements, overhead costs, and prevailing market factors. Table 1 compares average national wholesale prices of various fast-acting insulins (24). All the trade names compared are available over the

counter except for lispro insulin, which, at least for the present, requires a prescription. In addition, some healthcare plans, which consider lispro insulin to be nonformulary until it has undergone further review, do not cover it.

Table 1. Average national wholesale prices of various fast-acting insulins

Insulin	Price/10-mL vial (\$)
Pork Regular Iletin II	26.28
Humalog	24.98
Humulin R (human)	18.91
Novolin R (human)	18.91
Regular Iletin I (beef and pork)	16.09
Regular Purified Pork Insulin	26.66
Regular Insulin (pork)	14.34

Compiled from PriceAlert (24)

Conclusions

For many insulin-treated patients, lispro insulin (Humalog) offers increased convenience and flexibility in dosing (25). In addition to simplifying the lifestyle of diabetic patients who have achieved intensive control of the disease,

use of lispro insulin may allow control in many patients who have not previously been able to achieve and maintain control. Currently in development are other insulin analogues that are fast-acting (eg, ASPB28 human insulin) and long-acting (eg, neutral protamine lispro). Investigators are hopeful that a once-daily, very-long-acting, nonpeaking basal insulin will become available in the next several years. Lispro or another fast-acting insulin analogue could then be injected whenever food is ingested.

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