

Review Article

*Drug Therapy*ALASTAIR J.J. WOOD, M.D., *Editor***INSULIN LISPRO**FRITS HOLLEMAN, M.D.,
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THE difference in amino acid composition between beef and porcine insulins and human insulin was long thought to be responsible for the immunogenicity of these animal insulins in humans. As a result, much of the effort expended to meet the world's increasing demand for insulin was devoted to the development of synthetic human insulin. However, the introduction of highly purified synthetic human insulin in the early 1980s did not entirely solve the problem of immunogenicity, and the new technology was used instead to change the amino acid structure of human insulin to make it more suitable for subcutaneous administration. This led to the development of insulin analogues with pharmacokinetic characteristics that differed from those of regular human insulin. The first of these analogues to become available was insulin lispro, which was approved for clinical use in Europe in April 1996 and in the United States in June 1996. In this review we discuss the pharmacologic and clinical data on insulin lispro and its role in the treatment of patients with diabetes mellitus.

THE IMPERFECTIONS OF INTENSIVE INSULIN THERAPY

The results of several clinical trials, such as the Stockholm Diabetes Intervention Study and the Diabetes Control and Complications Trial (DCCT), have demonstrated that strict glycemic control in patients with insulin-dependent diabetes mellitus (IDDM) reduces the risk of complications such as retinopathy and nephropathy.^{1,2} In these studies control was usually achieved by continuous subcutane-

ous insulin infusion or by multiple daily subcutaneous doses of insulin.

In the regimen involving multiple daily doses, one or more subcutaneous doses of intermediate (isophane) or long-acting (zinc) insulin are combined with doses of regular insulin before each meal in an attempt to mimic physiologic insulin secretion.³ However, for several reasons, this regimen fails to achieve the intended effect. First, although intravenously administered regular insulin reaches peak serum concentrations in just a few minutes, the action of subcutaneously administered regular insulin reaches a maximum about two hours after injection, making it necessary to inject the insulin at least half an hour before the meal to limit the meal-related increase in serum glucose concentrations.^{4,5}

Second, the action of intravenously injected regular insulin lasts less than an hour, whereas that of subcutaneously injected insulin lasts several hours, which may lead to postprandial hyperinsulinemia and consequent hypoglycemia.⁶⁻⁸ Third, the subcutaneous route of administration results in higher peripheral serum insulin concentrations than does insulin secreted into the portal vein. Finally, when injected once daily, the intermediate and long-acting insulins do not provide an appropriate 24-hour basal serum insulin concentration.⁸ These problems are reflected in the fact that even in the DCCT the glycosylated hemoglobin values in most of the intensively treated patients were not within the normal range, whereas the incidence of severe hypoglycemia in this group was three times higher than that in the conventionally treated patients.^{2,9}

DEVELOPMENT OF INSULIN ANALOGUES

The problems described above have given impetus to efforts to find alternatives to regular insulin for injections before meals. Regular human insulin molecules form dimers in solution, and in the presence of zinc atoms these dimers associate to form hexamers (Fig. 1). Although insulin monomers and dimers diffuse rapidly from the subcutaneous space into the circulation, the size of the hexamers limits their diffusion. Thus, both the rather slow onset of action and the prolonged duration of action of subcutaneously injected regular insulin can be attributed to the tendency of molecules of regular insulin to associate.¹⁰

After synthetic human insulin was introduced, the amino acid structure of human insulin was modified to produce insulin analogues that remain monomeric or dimeric in solution.¹¹ Some of these analogues were tested clinically and were indeed ab-

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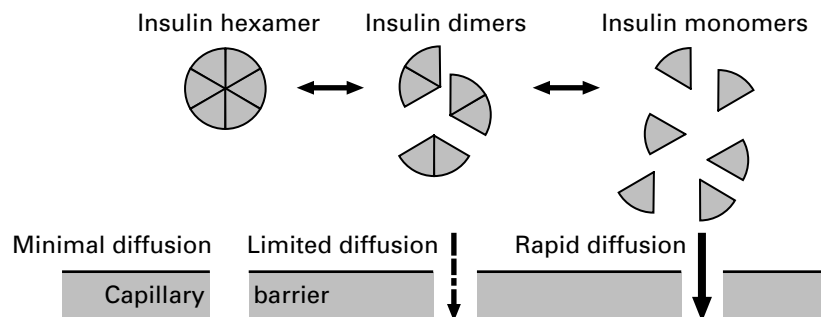


Figure 1. The Diffusion of Insulin.

Insulin molecules form dimers and hexamers in solution. The diffusion of the hexamers is limited by their size; dimers and monomers diffuse more rapidly.¹⁰

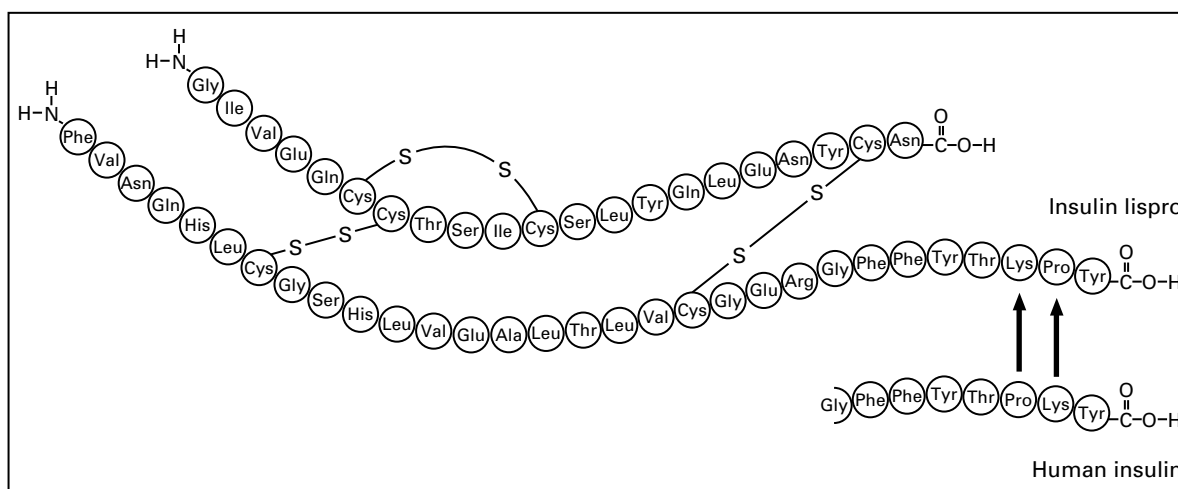


Figure 2. The Amino Acid Sequence of Insulin Lispro.

In insulin lispro (shown in full) the positions of proline at B28 and lysine at B29 at the C-terminal end of the B chain are reversed in comparison with human insulin (only C-terminal end shown).

sorbed more rapidly after subcutaneous injection than regular human insulin.¹²⁻¹⁵ However, most of the changes in the amino acid structure also altered biologic properties.¹⁶ For example, the analogue Asp^{B10} was found to have a carcinogenic effect that was subsequently attributed to an increased affinity of the analogue for the receptors of insulin-like growth factor I or a decreased rate of dissociation of the analogue from the insulin receptor, and clinical studies were halted.¹⁷⁻²⁰

STRUCTURE OF INSULIN LISPRO

It was the structural homology of insulin with insulin-like growth factor I that led to the development of insulin lispro. Insulin-like growth factor I,

although structurally similar to insulin, has little tendency to self-associate²¹ as a result of differences between the amino acid composition of the C-terminal end of its B chain and that of insulin.²²⁻²⁴ Several analogues based on amino acid substitutions in this region have been made. In insulin lispro (Lys^{B28},Pro^{B29} human insulin) the natural sequence of proline at position B28 and lysine at position B29 is reversed (Fig. 2). This reversal leads to a conformational shift in the C-terminal end of the B chain that sterically hinders the ability of the insulin monomers to form dimers. Thus, the dimer association constant is reduced by a factor of 300 as compared with that of regular insulin. The monomeric nature of insulin lispro at physiologic concentrations was

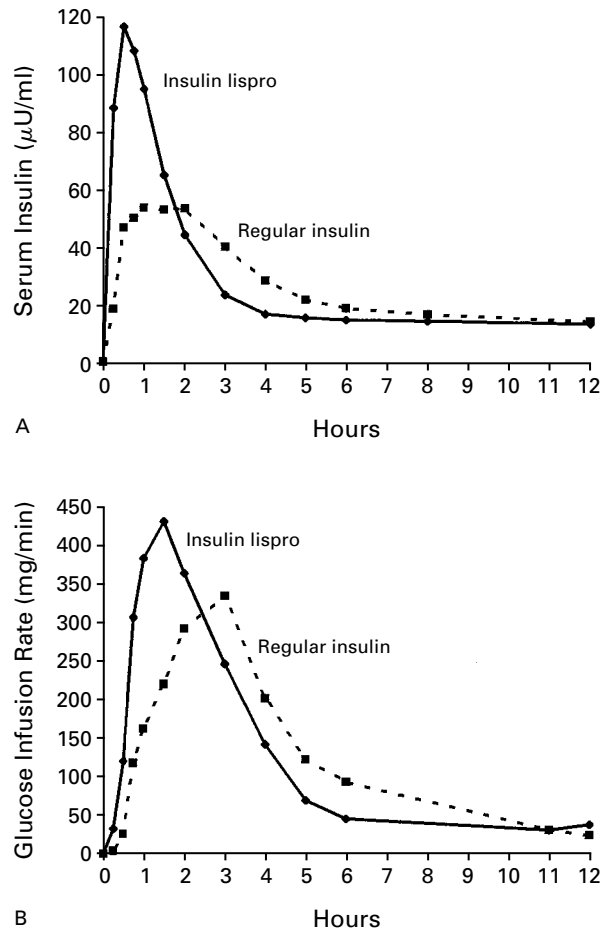


Figure 3. Effects of Subcutaneous Administration of Insulin Lispro and Regular Insulin on Serum Insulin Concentrations (Panel A) and the Rate of Glucose Infusion Necessary to Maintain Normoglycemia (Panel B) in 10 Normal Subjects.

To convert values for insulin to picomoles per liter, multiply by 6.0; to convert values for the glucose infusion rate to millimoles per minute, multiply by 0.005551. Data were adapted from Howey et al.³⁴

established by size-exclusion chromatography, circular dichroism studies, and ultracentrifugation.²⁵

BIOLOGIC ACTIONS OF INSULIN LISPRO

The reversal in the sequence of proline and lysine and the resulting conformational change do not affect the receptor-binding domain of the insulin molecule. The affinity of insulin lispro for the insulin receptor is similar to that of regular insulin.^{26,27} The affinity of insulin lispro for the receptor of insulin-like growth factor I is about 1½ times that of regular insulin, but only 0.1 percent of the affinity of the growth factor itself.^{26,27} Accordingly, *in vitro*, cell growth is stimulated to the same extent by regular insulin and insulin lispro.²⁷ Extensive studies in ani-

mals, including a reproductive and developmental study in rats, revealed no adverse events except those related to the hypoglycemic effect of the analogue.²⁸⁻³⁰ Finally, in a study in rhesus monkeys, IgG antibodies to insulin lispro developed in only 1 of 12 animals after immunization with insulin lispro in Freund's adjuvant, and the serum antibody concentrations in this animal were low.³¹

Studies in pigs indicated that subcutaneously injected insulin lispro was more rapidly absorbed into the circulation than regular insulin (90 percent absorption in 100 minutes, as compared with a time of 150 minutes for regular insulin). Insulin sensitivity and serum insulin concentrations were similar to those with regular insulin,³² and the results were similar in rats and dogs.³³

PHARMACOKINETICS OF INSULIN LISPRO

During a euglycemic clamp study in normal subjects, the peak serum insulin concentration was significantly higher (116 vs. 51 μU per milliliter [698 vs. 308 pmol per liter]) and earlier (42 vs. 101 minutes) after the subcutaneous administration of insulin lispro than after regular insulin (Fig. 3A).³⁴ The rates of glucose infusion needed to maintain euglycemia followed a similar pattern (Fig. 3B). The total hypoglycemic potency of insulin lispro was equivalent to that of regular insulin, and the systemic clearance rates of both types of insulin were similar. These results were confirmed in patients with IDDM,³⁵⁻³⁷ although in some studies the hypoglycemic potency of insulin lispro was slightly higher than that of regular insulin.^{36,37} The duration of action of insulin lispro (about three hours) is shorter than that of regular insulin (about five hours).³⁸

Many factors influence the absorption of insulin lispro from subcutaneous injection sites, just as they influence the absorption of regular insulin. For example, absorption is faster from the abdominal region than from the deltoid or femoral region,³⁵ and the rate of absorption is increased by heat.³⁹ These effects are, however, less pronounced for insulin lispro than for regular insulin.

The length of time to the peak activity after the subcutaneous injection of insulin lispro is independent of the dose, whereas the time to the peak activity of regular insulin increases with increasing doses.⁴⁰ The latter effect had been attributed to decreased perfusion of the injection site because of compression of capillaries by the increasing volume of injection,⁸ but in the light of these new data it is more likely to be due to the intrinsic properties of the insulins. The intrinsic properties of monomeric insulins may also contribute to the decreased variability in serum insulin concentrations in individual patients after the administration of insulin lispro as compared with regular insulin (9.9 percent vs. 23.8 percent).⁴¹ After intraperitoneal administration, the

TABLE 1. STUDIES COMPARING INSULIN LISPRO AND REGULAR INSULIN GIVEN IN REGIMENS INVOLVING MULTIPLE DAILY DOSES AMONG PATIENTS WITH DIABETES MELLITUS.*

STUDY	NO. OF PATIENTS AND TYPE OF DIABETES	STUDY DESIGN	DURATION OF TREATMENT	PERCENT DIFFERENCE IN GLYCOSYLATED HEMOGLOBIN VALUES	PERCENT DIFFERENCE IN FREQUENCY OF HYPOGLYCEMIA	DIFFERENCE IN 2-Hr POSTPRANDIAL INCREASE IN GLUCOSE (mg/dl)†	DIFFERENCE IN FASTING GLUCOSE CONCENTRATIONS (mg/dl)‡
Martin and Anderson ⁴⁷	78, IDDM 28, NIDDM	Crossover	3 mo	None -0.3	-3‡	-47 -43	NA
Vignati et al. ⁴⁸	336, IDDM 295, NIDDM	Parallel	1 yr	-0.2 (P=0.17)	None	-20 (P=0.007)	NA
Vignati et al. ⁴⁹ §	167, IDDM	Parallel	1 yr	-0.2 (P=0.03)	None	-50 (P=0.001)	+7 (P=0.50)
Anderson et al. ⁵⁰ §	145, NIDDM	Parallel	1 yr	-0.2 (P=0.69)	-16 (P=0.51)	-25 (P=0.02)	+5 (P=0.53)
Anderson et al. ⁵¹	1008, IDDM	Crossover	3 mo	None	-12 (P=0.001)	-36 (P<0.001)	NA
Brunelle et al. ⁵²	722, NIDDM	Crossover	3 mo	None	-4 (P=0.31)	-29 (P<0.001)	+9 (P=0.002)
Garg et al. ⁵³	37, IDDM	Parallel	1 yr	+0.2	None	-72 (P<0.05)	-2
Pfützner et al. ⁵⁴	104, IDDM	Crossover	3 mo	None	-11 (P=0.008)	-31 (P<0.001)	NA
Schmitt et al. ⁵⁵	199, IDDM	Crossover	3 mo	None	-4	-32 (P<0.001)	+7 (P=0.08)
Rowe et al. ⁴⁶	93¶	Blinded, crossover	3 mo	None	None	-32 (NA)	+13 (P=0.02)

*All differences are the differences between treatment with insulin lispro and treatment with regular insulin. IDDM denotes insulin-dependent diabetes mellitus, NIDDM non-insulin-dependent diabetes mellitus, and NA not available.

†To convert values for glucose to millimoles per liter, multiply by 0.05551.

‡This value refers to both the patients with IDDM and those with NIDDM.

§Data from this study were included in the overall analysis in Vignati et al.⁴⁸

¶The type of diabetes was not clearly specified.

pharmacokinetics of insulin lispro and regular insulin are similar.⁴²

CLINICAL STUDIES OF INSULIN LISPRO

Over 4000 patients with diabetes have received insulin lispro in various studies. Most studies compared insulin lispro with regular insulin in a regimen involving multiple daily doses. As a result of its more rapid onset of action, insulin lispro must be injected just before a meal, whereas regular insulin should be injected at least half an hour before a meal.⁴³⁻⁴⁵ This difference in the time of injection has been the reason that most clinical studies, although randomized, have been open-label. The results from the only published double-blind study were similar to those of the open-label studies.⁴⁶

The results of the randomized studies are summarized in Table 1.⁴⁷⁻⁵⁵ In these studies meal-related increases in glucose concentrations were 20 to 72 mg per deciliter (1 to 4 mmol per liter) lower in the patients using insulin lispro than in those using regular insulin. The fasting glucose concentrations and the glucose concentrations measured before meals tended to be higher during treatment with insulin lispro than during treatment with regular insulin. This pattern can be explained by the low serum insulin concentrations that are the result of the too-short duration of action of the basal insulins (e.g., nighttime insulin isophane) given to all patients. Previously

this shortcoming was masked by the long duration of action of regular insulin. It is therefore not surprising that glycosylated hemoglobin values did not decrease during therapy with insulin lispro.

Interestingly, in a recent sequential study in nine patients with IDDM, the introduction of insulin lispro was not followed by a decrease in glycosylated hemoglobin values, whereas the subsequent introduction of a second dose of insulin isophane was followed by a significant (2 percent) decrease in glycosylated hemoglobin.⁵⁶ Likewise, mixing insulin lispro with small quantities of insulin isophane improves the overall glycemic profile in patients with IDDM.⁵⁷ Body weight increases during intensification of treatment, but not more for insulin lispro than for regular insulin.⁵⁴

In patients with IDDM, the frequency of hypoglycemia is somewhat lower during treatment with insulin lispro than during treatment with regular insulin (Table 1). In the largest crossover study there was a 12 percent decrease in the total number of episodes of hypoglycemia.⁵¹ In a study of patients with well-controlled IDDM (mean base-line glycosylated hemoglobin value, 7.3 percent) the number of severe episodes, as defined by DCCT criteria, was lower in the insulin lispro group (58 vs. 36, P=0.04), but the overall frequency of hypoglycemia in the two groups was similar.⁵⁵

In patients with non-insulin-dependent diabetes

TABLE 2. ADVANTAGES AND DISADVANTAGES OF INSULIN LISPRO THERAPY.***Advantages**

Reduced postprandial increases in blood glucose concentrations⁴⁶⁻⁵⁵
 Reduced frequency of hypoglycemia in patients with IDDM^{49,51,54,55}
 Greater convenience for patients in terms of the interval between injections and meals^{5,54,55,69,70}

Potential advantages

Improved glycemic control in patients receiving continuous subcutaneous infusion⁵⁹
 Decreased variability in serum insulin concentrations in individual patients⁴¹
 Treatment of antibody-mediated resistance to regular human insulin⁷⁶⁻⁷⁸
 More physiologic serum insulin profile^{34-36,57}

Potential disadvantages

Low basal serum insulin concentrations
 More rapid onset of ketoacidosis in the case of pump failure in patients receiving continuous subcutaneous infusion⁶⁰
 Unknown teratogenicity and long-term safety profile
 Higher cost

*IDDM denotes insulin-dependent diabetes mellitus.

mellitus, the frequency of hypoglycemia is not altered by insulin lispro. One study suggested that a reduction in the rate of hypoglycemia might be achieved in patients with non-insulin-dependent diabetes mellitus who were at high risk of hypoglycemia,⁵⁸ but these results have not been confirmed.

A few studies have evaluated insulin lispro in other insulin regimens. The initial results in patients treated by a continuous subcutaneous infusion of insulin are promising. In a double-blind crossover study in 30 patients with IDDM, the glycosylated hemoglobin values (7.7 percent vs. 8.0 percent, $P=0.004$) and postprandial increases in serum glucose were lower during treatment with insulin lispro than during treatment with regular insulin.⁵⁹ The frequency of hypoglycemia was similar during the two treatments. The glucose concentrations measured before breakfast and in the evening were lower during insulin lispro treatment, once more underlining the importance of maintaining normal basal serum insulin concentrations — for example, by a continuous subcutaneous infusion.

A disadvantage of insulin lispro in patients who are receiving a continuous subcutaneous insulin infusion may be the more rapid onset of ketoacidosis (four hours, as compared with six hours with regular insulin) in the case of pump malfunction.⁶⁰ The extent of the precipitation and degradation of insulin lispro in the infusion system is similar to that of regular insulin.^{60,61} The twice-daily administration of mixtures of insulin lispro and insulin isophane results in a level of glycemic control that is similar to that produced by mixtures of regular insulin and insulin isophane.^{62,63}

Awareness of Hypoglycemia

The introduction of regular human insulin led to suggestions that patients' awareness of hypoglycemia decreased after those who had been receiving porcine insulin began to use human insulin.⁶⁴ Although conclusive evidence to the contrary was ultimately reported,^{65,66} some patients still hesitate to take novel insulins for this reason. Studies of the awareness of hypoglycemia and of counterregulation after the administration of insulin lispro have revealed similar counterregulatory hormone responses, neuroglycopenic symptoms, and autonomic symptoms after the administration of insulin lispro and regular human insulin.^{36,67,68} The earlier onset of hypoglycemia that is the result of the rapid action of insulin lispro may result in an earlier onset of symptoms.

Quality of Life

Due to the open nature of most studies of insulin lispro, the reliability of all quality-of-life data is limited. Nevertheless, in some studies insulin lispro was associated with a significant increase in patients' overall satisfaction with treatment as compared with regular insulin.^{54,55} In particular, patients considered the opportunity to inject insulin lispro immediately before a meal an advantage, and they reported increased flexibility and freedom in daily activities.⁶⁹ In several studies a majority of patients who were receiving regular insulin did not follow instructions to inject the insulin 30 to 60 minutes before eating, thus expressing their preferences for injection just before the meal.^{5,55,70}

Safety and Immunogenicity

No differences have been reported between insulin lispro and regular insulin with respect to the likelihood of allergic reactions, adverse events, and abnormal laboratory values.⁷¹ Pregnancy was an exclusion criterion in all studies, and therefore, no data are available on the use of insulin lispro during pregnancy. The safety of insulin lispro in adolescents is similar to that of regular insulin,⁷² but data on younger children are not available.

The immunogenicity of insulin lispro is similar to that of regular insulin.^{73,74} In patients who had not previously been exposed to insulin, there was a slightly higher frequency of the induction of insulin antibodies in patients using insulin lispro than in those using regular insulin. However, the difference was significant in patients with non-insulin-dependent diabetes mellitus only after six months of treatment; after a year, the percentage of patients with antibodies was similar in the two groups. Specific antibodies against insulin lispro hardly ever develop, and insulin dose requirements have not been affected by antibody formation.⁷⁵ There are several case reports of patients in whom severe antibody-mediated resistance to regular human insulin was successfully treated by switching to insulin lispro.⁷⁶⁻⁷⁸ These

patients did have cross-reacting insulin antibodies, and therefore the underlying mechanism is unclear.

GUIDELINES FOR THE USE OF INSULIN LISPRO

Many factors determine the degree of glycemic control in patients with diabetes. Patient-related factors, such as motivation and knowledge of the disease, are probably more important than the type of insulin or the insulin regimen used. Thus, although insulin lispro has some small advantages over regular insulin, it will not greatly alter glycemic control in most patients with diabetes. The advantages and disadvantages of insulin lispro therapy are summarized in Table 2.

In women of child-bearing age, the paucity of data regarding possible side effects thus far restricts the use of insulin lispro unless adequate contraception is guaranteed. Likewise, data on the safety of insulin lispro in children under 10 years of age have not yet been published.

Insulin lispro therapy probably has no advantage in patients with high glycosylated hemoglobin values because these patients rarely have hypoglycemia and insulin lispro does not improve glycosylated hemoglobin values. These patients benefit more from other interventions, such as intensification of education about their illness, home monitoring of blood glucose concentrations, and the use of pen devices for insulin administration.

In our opinion, several groups of patients may benefit from treatment with insulin lispro. Among them are patients with IDDM and low glycosylated hemoglobin values who have a high risk of hypoglycemia (as was demonstrated in the DCCT^{2,9}). Patients who lead active lives may appreciate the increased flexibility that the shorter action profile of insulin lispro offers. Finally, patients with recent-onset IDDM who have some residual β -cell function to provide basal insulinemia between meals are also good candidates for the use of insulin lispro.⁴⁵

The regimen of choice when one is initiating insulin lispro therapy is one involving multiple daily doses with insulin isophane given in the evening. It may, however, be necessary to inject a second dose of insulin isophane in the morning to preclude insufficient basal serum insulin concentrations and consequent hyperglycemia in the late afternoon and evening (Fig. 4).^{55,56} The initial dose of insulin lispro can be identical to the dose of regular insulin given previously, but slight adjustments in the dose may be necessary.

It is important to instruct patients carefully about the action profile of insulin lispro. In our experience, patients treated with insulin lispro who have blood glucose concentrations of 72 to 90 mg per deciliter (4 to 5 mmol per liter) about three hours after a meal may, because they are accustomed to the action profile of regular insulin, snack unnecessarily for fear of a late hypoglycemic reaction. In patients using in-

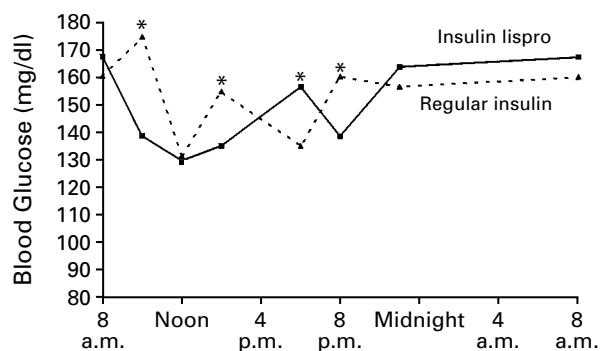


Figure 4. Glycemic Profiles of Regimens Involving Multiple Daily Doses with an Evening Dose of Insulin Isophane and Three Injections of Either Insulin Lispro or Regular Insulin in 189 Patients with Insulin-Dependent Diabetes Mellitus.

Blood glucose concentrations before meals, two hours after meals, and at bedtime were plotted on the basis of mealtimes of 8 a.m., noon, and 6 p.m. Asterisks denote $P < 0.001$ for the comparison between groups. To convert values for glucose to millimoles per liter, multiply by 0.05551.

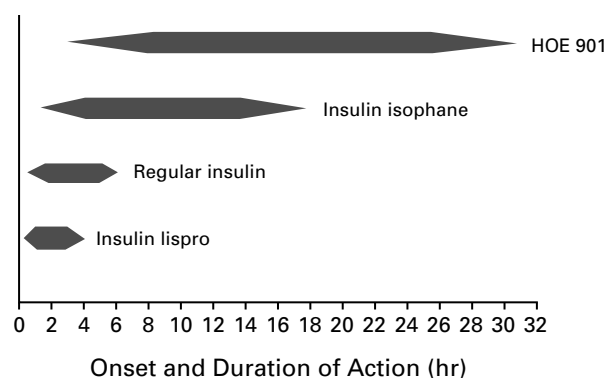


Figure 5. Onset and Duration of Action of Types of Insulin and Insulin Analogues.

HOE 901 is an investigational insulin analogue with a prolonged duration of action.

ulin lispro, exercise shortly after a meal increases the risk of hypoglycemia, whereas in patients using regular insulin, exercise several hours after the meal poses the greater risk.³⁷

FUTURE PROSPECTS

Insulin lispro is currently used mainly in regimens involving multiple daily doses. As discussed earlier, the relatively short duration of action of insulin isophane may be the main reason that the advantages of insulin lispro do not lead to improved glycosylated hemoglobin values. Therefore, the combination of insulin lispro and a really long acting insulin analogue could be useful. The respective action profiles of these types of insulin are shown in Figure 5.

Currently, the insulin analogue HOE 901 (Gly^{A21-}

di-arginyl^{B30}-human insulin, Hoechst) is the most likely candidate to meet these basal insulin requirements, but other basal insulin analogues are being developed.⁷⁹⁻⁸¹ A protamine formulation of insulin lispro with prolonged action (NPL) has been developed.^{82,83} This development opens the way to the use of mixtures of insulin lispro with NPL in regimens involving two daily injections. These mixtures are similar to mixtures of regular insulin and insulin isophane but have a more rapid onset of action, which might in turn diminish the increase in blood glucose concentrations that occurs after breakfast and dinner.⁸⁴

CONCLUSIONS

Insulin lispro is appealing in principle, but the advantages of this drug over regular human insulin thus far seem limited to a slight decrease in the frequency of hypoglycemia, greater convenience in the timing of administration, and possibly, a decrease in glycosylated hemoglobin when the drug is given by continuous subcutaneous infusion. In other regimens glycosylated hemoglobin values are not affected, apparently because lower postprandial glucose concentrations are counterbalanced by higher preprandial and nighttime glucose concentrations. Properly randomized long-term studies with insulin lispro, which carefully examine the frequency of hypoglycemia, glycosylated hemoglobin values, and glycemic profiles, are needed to determine whether increases in basal insulin levels could overcome these problems. Given the available data, a patient should be treated with insulin lispro only after careful consideration of his or her overall situation, because patient-related factors will generally have a greater impact on glycemic control than the type of insulin used.

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