Rationale for the Development and Clinical Use of

Insulin Analogs & Premixed Insulin Analogs

A continuing education monograph for pharmacists, nurses, and dietitians
this CE activity can also be completed on-line at www.MedEdToday.com.

This activity is supported by an educational grant from Novo Nordisk Inc.
It has been accredited by AADE for pharmacists, nurses, and dietitians.

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Program Goal

To provide healthcare professionals with a summary of the development, efficacy, and safety of insulin analogs and premixed insulin analogs and a general guide for the proper clinical use of these formulations.

Target Audience

This activity has been designed to meet the educational needs of pharmacists, nurses, and dietitians involved with the management of patients with diabetes.

Educational Objectives

After reading this monograph, the participant should be able to:

- Explain the rationale for the development of insulin analogs and premixed insulin analogs.
- Describe the molecular alterations of rapid- and long-acting insulin analogs.
- State the major differences between the time-action profiles of insulin analogs, premixed insulin analogs, and human insulin formulations.
- Describe how insulin analogs are manufactured.
- Identify major considerations when individualizing treatment with insulin analogs or premixed insulin analogs.

Fee

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Introduction

Since insulin was first used in 1922 for the treatment of diabetes, the inability to mimic normal physiological secretion has been a major limitation for achieving optimal glycemic control. Therefore, considerable research has been undertaken to develop insulin formulations that have more physiological time-action profiles to cover basal and prandial needs. Although human insulin formulations produced by recombinant DNA technology were a significant advance over animal insulin isolated from pancreatic tissue, therapy still resulted in a delayed onset and prolonged duration of action of bolus insulin, and variable peaks and troughs with basal insulin. To overcome these limitations, insulin analogs and premixed insulin analogs have been developed in an attempt to mimic the insulin secretion patterns found in individuals without diabetes (ie, produce elevations in blood insulin that peak earlier and fall more rapidly after meals, or maintain a low steady-state level of insulin between meals to cover basal needs). A decrease in overall variability in insulin absorption and action has also been a major goal. This program examines the need for insulin formulations with more physiological time-action profiles and their role in achieving optimal glycemic control.

The Clinical Need for New Insulin Preparations

Normal Insulin Secretion

Insulin is the key metabolic hormone that regulates the utilization of energy between and after meals. Pancreatic beta cells secrete insulin in two different ways: 1) basal secretion - slow, steady level between meals or snacks to allow sufficient hepatic glucose production to maintain blood glucose (BG) levels above 60 mg/dL; and 2) prandial secretion - rapid increase in insulin levels to distribute the ingested carbohydrate to the peripheral tissues, stop hepatic glucose production, and prevent exaggerated postprandial blood glucose levels. Secretion of endogenous insulin is tightly correlated with BG levels and ensures that they do not drop too low between meals (basal secretion) and that they increase enough after meals (prandial secretion). If a fast is prolonged, basal insulin levels drop even lower allowing lipolysis in the adipocytes and ketogenesis in the liver. A normal 24-hour physiological profile of insulin secretion can be summarized as shown in Figure 1.

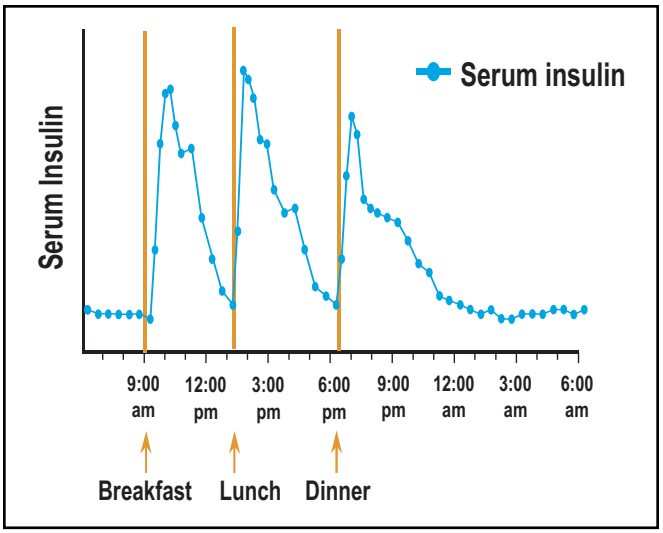

Figure 1. Physiological Profile of Insulin Secretion: Healthy Subjects.

Insulin secretion at mealtimes normally occurs in two phases: an early, tall burst of "first-phase" insulin secretion, followed by a smaller but sustained peak of "second-phase" postprandial secretion. The first phase lasts only 20 to 30 minutes and consists of a very rapid spike secreted in the portal circulation. The main effect of the first phase of prandial insulin secretion is to abolish the production of glucose in the liver. The second phase of insulin secretion is of lower magnitude and lasts for 2 to 3 hours to minimize the postprandial glycemic excursion.

The prevention of hypoglycemia between meals is very important to assure continuous supply of glucose, mostly to the brain. The prevention of hyperglycemia after meals, and between meals, is also important to prevent many serious long-term microvascular and macrovascular complications (glucotoxicity). The proper supply of insulin at all of these different feeding and metabolic moments is very important for reaching target BG levels and avoiding glycemic levels that are too low or too high.

Insulin Secretion in Diabetes

Type 1 diabetes is characterized by absolute insulin deficiency due to the autoimmune destruction of pancreatic beta cells,[1] resulting in the loss of at least 50 to 80% of insulin production.[2] Patients with type 1 diabetes therefore require exogenous insulin from the time of diagnosis. About 5% to 10% of individuals with diabetes have type 1 diabetes.

Type 2 diabetes is a metabolic disease with two pathogenic factors: 1) insulin resistance - decreased levels of sensitivity to insulin action; and 2) beta-cell dysfunction - inability of the beta cell to compensate for the insulin resistance with a relative deficiency in insulin secretion, initially, but later on with an absolute deficiency of insulin (insulinopenia).[1] Type 2 diabetes accounts for 90% to 95% of all cases diagnosed.[3] The beta-cell dysfunction of type 2 diabetes is progressive with a continuous decline in insulin secretion over the years leading to higher and higher levels of BG. Early stages of beta-cell dysfunction are characterized by the loss of the first phase of prandial insulin secretion (Figure 2).[4] This is accompanied by increased postprandial glycemic levels. As type 2 diabetes progresses, with the progressive decline in beta-cell function (40% to 60%),[5] accompanied by amyloid deposits in the pancreatic islets,[6] fasting BG also increases. Although the initial insulin deficiency is relative in type 2 diabetes, it worsens over the years because of progressive beta-cell loss, and most patients with type 2 diabetes eventually require insulin therapy.

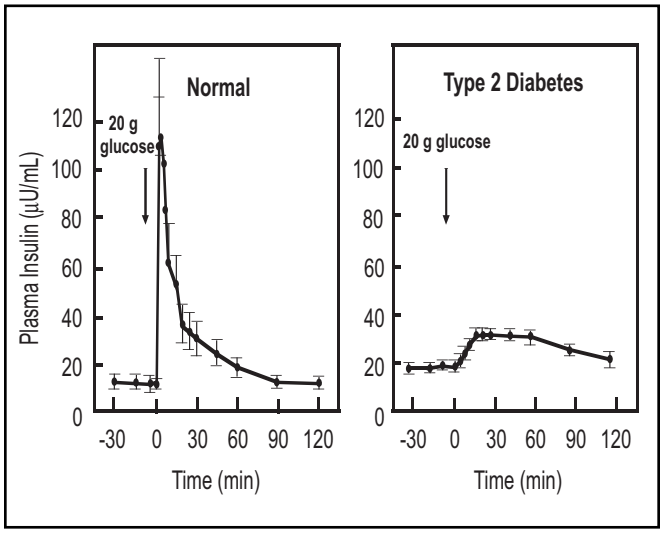

Figure 2. Loss of Early-Phase Insulin Secretion in Type 2 Diabetes.
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Ward WK et al. *Diabetes Care*. 1984:491-502.[4]
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Diabetes can also develop during pregnancy (gestational diabetes mellitus, GDM). GDM is usually diagnosed by an oral glucose tolerance test in women with risk factors including obesity, strong family history of diabetes, glycosuria, or previous GDM.[7] In the United States, GDM develops in 7% of pregnant women resulting in more than 200,000 cases per year.[7]

A pregnant woman with diabetes has a significantly increased risk of maternal and fetal/neonatal morbidity and mortality if glucose levels are not well controlled. Hypertension, dyslipidemia, and other comorbidities should be managed as well. Women diagnosed with GDM have a 20% to 50% risk of developing diabetes within 5 to 10 years,[3] though they usually return to the euglycemic state after delivery.

Glycemic Control and Complications from Diabetes

Results from the Diabetes Control and Complications Trial (DCCT) indicated that optimal control of blood glucose and A1C levels was associated with a significant decrease in the microvascular complications of diabetes (retinopathy, neuropathy, and nephropathy).[8] In patients with type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) also showed that a reduction of A1C was similarly associated with a reduced incidence of microvascular complications.[9]

Although fasting plasma glucose (FPG) is commonly used to diagnose diabetes,[10] postprandial hyperglycemia occurs early during the development of type 2 diabetes and is a major contributor to the A1C increase in patients with diabetes.[11] Numerous epidemiological studies over the past 25 years have shown that postprandial hyperglycemia is also a major risk factor for developing cardiovascular disease, the leading cause of mortality in patients with type 2 diabetes.[12]

The DECODE study (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) investigated the mortality rates among 13 prospective European cohorts over 7 years in relation to FPG and postprandial glucose (PPG), 2 hours after a 75-gram oral glucose tolerance test.[13] The investigators concluded that FPG alone does not identify all individuals at increased risk of cardiovascular death. For any given range of FPG values, there was a higher mortality rate with increasing 2-hour PPG plasma values, even in persons without overt diabetes. When screening individuals for hyperglycemia it is important to measure PPG to detect individuals with impaired glucose tolerance because it is the greatest attributable risk factor for death associated with hyperglycemia.[13]

Mimicking Normal Secretion by Subcutaneous Injection: Basal and Prandial Insulin

For patients with either type 1 or advanced type 2 diabetes, the ideal insulin regimen not only controls FPG levels and reduces A1C values, but also controls post-

prandial glycemic excursions. To do so, a regimen must include basal and prandial (bolus) insulin, with the aim of mimicking normal beta-cell secretion (Figure 3). Borrowing from insulin pump terminology, the administration of basal insulin between meals and a "bolus" of insulin just prior to meals is called "basal-bolus" therapy. The postprandial glucose peak is controlled by a mealtime injection of insulin having a rapid onset and relatively short duration of action. The basal insulin in this treatment regimen provides a slow, steady level of insulin during between-meal periods and at night.

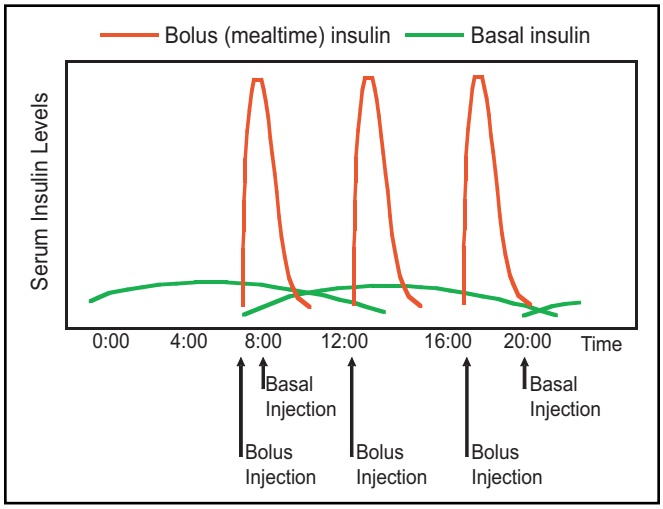

Figure 3. Approximation of the Normal Insulin Secretion Profile by a Basal-Bolus Insulin Injection Regimen.

Until 1996, soluble formulations of "regular" human insulin, such as Humulin® R (human insulin [rDNA origin] injection) and Novolin® R (human insulin [rDNA origin] injection), were the most rapid-acting formulations available and were used as bolus insulin before meals. Unfortunately, regular human insulin crystallizes in a hexameric form, which is physiologically inactive (cannot enter circulation) until it dissociates into monomers or dimers following subcutaneous injection.[14] The required dissociation into monomers is slow and delays the absorption of insulin from the subcutaneous site of injection. Therefore, to match the peaks of insulin and glucose following a meal, regular human insulin is injected at least 30 minutes prior to each meal. Patients often found it difficult to comply with the recommendation to inject 30 minutes before meals, increasing the potential for error. Furthermore, the duration of action of regular human insulin may be as long as 8 hours. Because postprandial glucose elevations do not last that long, hypoglycemic episodes between meals can result unless carefully timed snacks are added.

Basal insulin formulations have typically relied on crystalline suspensions of human insulin with Neutral Protamine Hagedorn (NPH) insulin, such as Humulin® N (human insulin isophane injection [rDNA origin]) and Novolin® N (human insulin isophane injection [rDNA origin]). NPH insulin formulations must be adequately resuspended before injection to ensure reproducible dose delivery, and crystalline material is inherently variable in dissolution from subcutaneous injection sites. Since patients may or may not properly follow resuspension instructions, the absorption of such basal insulin from injection sites is variable. NPH insulin therefore has a high day-to-day variability.[15] As intensive insulin therapy has become increasingly more common, more consistent insulin preparations are needed. Reducing the day-to-day variability in glucose-lowering effects of an insulin injection allows better glycemic control with a lower hypoglycemic risk.

Development of Insulin Analogs

Modifications of the Insulin Sequence to Alter the Time-Action Profile

It has become apparent that the pharmacokinetics of insulin formulations can be altered by bioengineered modifications of the natural amino acid sequence to produce "insulin analogs." Selective modifications of the native insulin molecule alter insulin pharmacokinetics following subcutaneous injection. This can either decrease (rapid-acting insulin analogs eg, aspart, glulisine, lispro), or increase (long-acting insulin analogs eg, detemir, glargine) the absorption time from the subcutaneous tissue with the corresponding changes in the time-action profile.[16]

Insulin lispro (Humalog®), insulin aspart (NovoLog®), and insulin glargine (Lantus®) are all currently marketed in the United States. Insulin glulisine (Apidra®) was approved by the US Food and Drug Administration (FDA) in 2004. Insulin detemir (Levemir®) is currently marketed in many European countries and was approved by the FDA in June 2005.

In both insulin lispro and aspart, the carboxy terminal end of the B-chain (residue 28 and 29 in lispro and residue 28 in aspart) has been changed.[17,18] The sequence modifications incorporated in these rapid-acting insulin analogs are summarized in Figures 4A and 4B. In insulin glulisine (Figure 4C), asparagine has been replaced by lysine at position B3 and lysine has been replaced by glutamic acid at B29.[19]

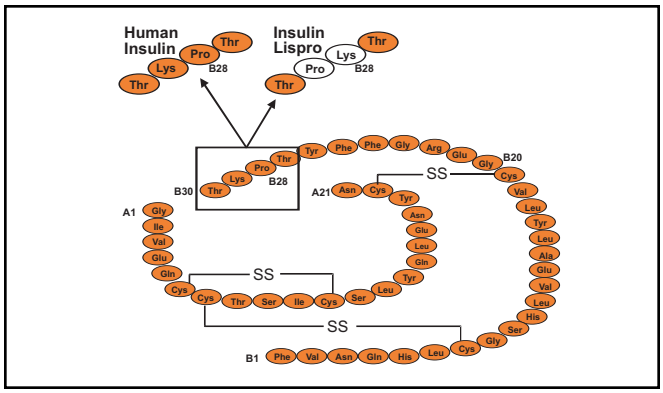

Figure 4A. Modifications of the Insulin Sequence in Insulin Lispro.

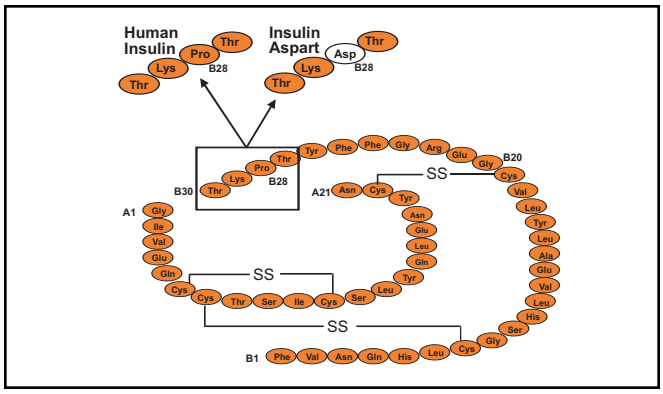

Figure 4B. Modifications of the Insulin Sequence in Insulin Aspart.

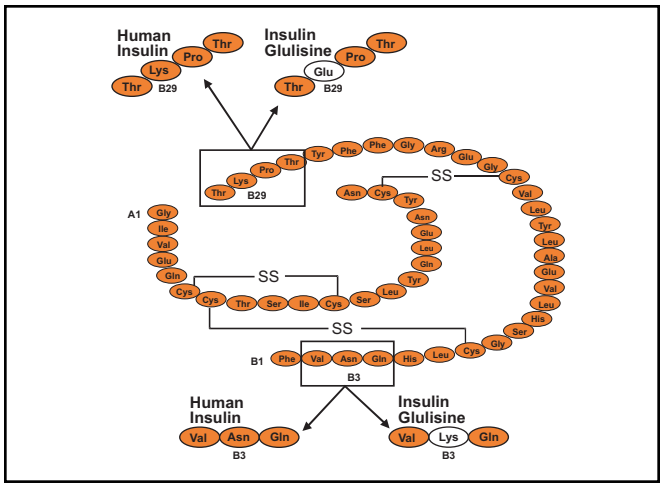

Figure 4C. Modifications of the Insulin Sequence in Insulin Glulisine.

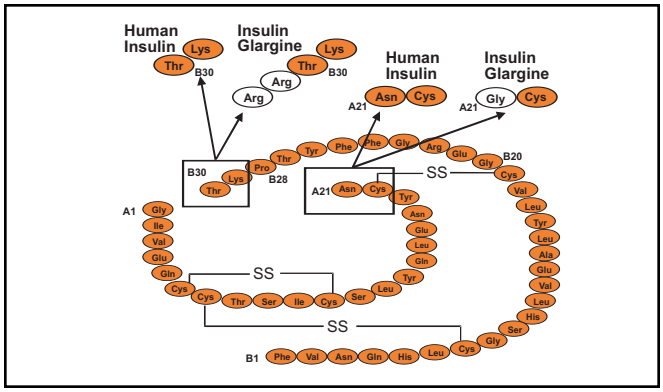

Figure 4D. Modifications of the Insulin Sequence in Insulin Glargine.

The altered pharmacokinetic behavior of rapid-acting insulin analogs is summarized in Figure 5. Following subcutaneous injection, rapid-acting insulin analogs in the subcutaneous depot have a reduced tendency for association as hexamers compared to regular human insulin.[20] For this reason, injected rapid-acting insulin analogs reach the circulation more rapidly than regular human insulin. Rapid-acting insulin analogs should not be mixed with other insulin formulations before injection unless clinical studies have established that predictable glucose-lowering effects may be achieved.

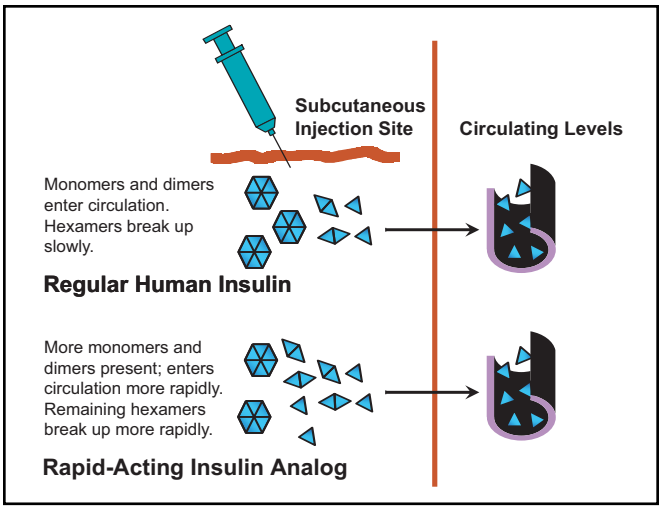

Figure 5. Pharmacokinetic Behavior of Rapid-Acting Insulin Analogs.

Amino acid sequence modifications can also fundamentally alter the electrical charge and solubility of the insulin molecule, making it suitable for use as long-acting basal insulin, as in the case of insulin glargine[21] (Figure 4D). Insulin glargine has a glycine residue in position A21 instead of the natural residue asparagine, as well as the addition of two arginine residues in positions B31 and B32. The latter modifications result in a significantly more positive charge, making it soluble in acidic pH ranges, but allowing it to precipitate at the neutral pH of the subcutaneous injection site. Injected insulin glargine forms a subcutaneous precipitate that is slowly absorbed into the circulation, leading to a prolonged duration of action. The acidic pH of insulin glargine makes it more precipitable when mixed with other insulin formulations, so mixing with other insulin formulations is not recommended.

Sequence modifications have been taken a step further with insulin detemir. A C14 fatty acid moiety (myristic acid) has been added to the B-chain lysine residue at B29, after the end threonine at position B30 has been

removed (Figure 6). Unlike insulin glargine and NPH insulin, insulin detemir is soluble at neutral pH; this enables it to exist as a liquid following subcutaneous injection.[22] The protracted action occurs through self-association of insulin molecules at the site of injection, and through reversible binding to albumin,[22] which provides longer permanence in the circulation.[23] This novel mechanism of protraction may contribute to lower intrasubject variability of insulin detemir compared with NPH insulin and insulin glargine in patients with type 1 diabetes.[24]

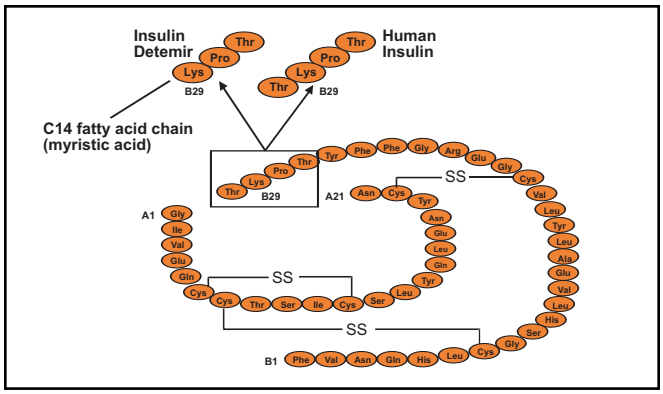

Figure 6. Modifications of the Insulin Molecule in Insulin Detemir.

Production Methods for Insulin Analogs

Production of recombinant proteins generally involves insertion of the recombinant DNA that encodes the new product in an expression organism, which is then produced on a large scale by fermentation processes. The recombinant DNA is typically introduced to the carrier cell as a self-replicating nonchromosomal DNA element known as a plasmid. Translation of the genetically modified DNA in the host cell produces the desired protein, which must then be collected, processed, and purified. In the case of insulin products, a high degree of purity must be achieved to reduce antibody formation.

Insulin Lispro

The modified sequence of human proinsulin (precursor of insulin) is inserted into nonpathogenic *Escherichia coli* bacterial cell line.[17] The proinsulin in this process is contained within the bacterium, so that the organism must be ruptured to recover the product. The proinsulin isolated from bacterial lysis must then be processed to remove the C-peptide. The resulting insulin lispro is subsequently purified. The final process for removal of possible *Escherichia coli* contaminants is sufficient to guarantee a very low level of antigenicity in the final product. The pH of the insulin lispro formulation is 7.0 to 7.8. The resulting product is a clear solution.

Insulin Aspart

Insulin aspart is manufactured by the insertion of a recombinant DNA plasmid into baker's yeast, *Saccharomyces cerevisiae*.[18] Like insulin lispro, the recombinant DNA encodes the proinsulin form of insulin aspart, which is isolated from the fermentation. The resulting proinsulin is secreted from the organism. Therefore, rupturing of the yeast cell is not necessary to retrieve the product. The product is then proteolytically cleaved to produce insulin aspart. The process for removal of possible *Saccharomyces cerevisiae* contaminants is sufficient to guarantee a very low level of antigenicity in the final product. The pH of the insulin aspart formulation is 7.2 to 7.6. The resulting product is a clear solution.

Insulin Glulisine

Similar to insulin lispro, insulin glulisine is manufactured by recombinant DNA technology using a nonpathogenic *Escherichia coli* (K12) bacterial cell line. The pH of the insulin glulisine formulation is approximately 7.3 and the resulting product is a clear solution.[19]

Insulin Glargine

Insulin glargine is also produced by recombinant technology, using a nonpathogenic strain (K12) of *Escherichia coli* as the production organism. Manufacturing of this long-acting insulin analog is conducted much like insulin aspart as described above. This proinsulin produced is then proteolytically cleaved and purified to generate the eventual product. The final formulation of insulin glargine is unusually acidic (pH approximately 4) to ensure that the analog product remains in solution until injection. Insulin glargine is a clear solution, not a suspension.

Insulin Detemir

Insulin detemir is produced by a process using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*). The C14 fatty acid side chain is attached to lysine at position B29 in the molecule by an acylation reaction. The formulation of insulin detemir is a clear, colorless, neutral solution (pH 7.4).

Pharmacokinetics and Pharmacodynamics of Insulin Analogs

Rapid-Acting Insulin Analogs

Pharmacokinetic studies of rapid-acting insulin analogs typically show a rapid entry into the circulation. However, elimination of rapid-acting insulin analogs from the circulation occurs at a rate that is essentially identical to elimination of short-acting regular human insulin. Because a rapid-acting insulin analog is absorbed into the circulation faster, the net effect is that peak serum concentrations of the insulin analog appear much earlier than regular human insulin.

In a pharmacokinetic analysis of insulin lispro, 10 subjects with type 1 diabetes received a subcutaneous injection (mean dose = 15.4 units) of either insulin lispro or regular human insulin immediately before a high-carbohydrate test meal.[17] Peak levels of insulin lispro occurred approximately 20 to 30 minutes earlier than regular human insulin, and serum insulin levels returned to baseline approximately 1 hour earlier than regular human insulin (Figure 7).

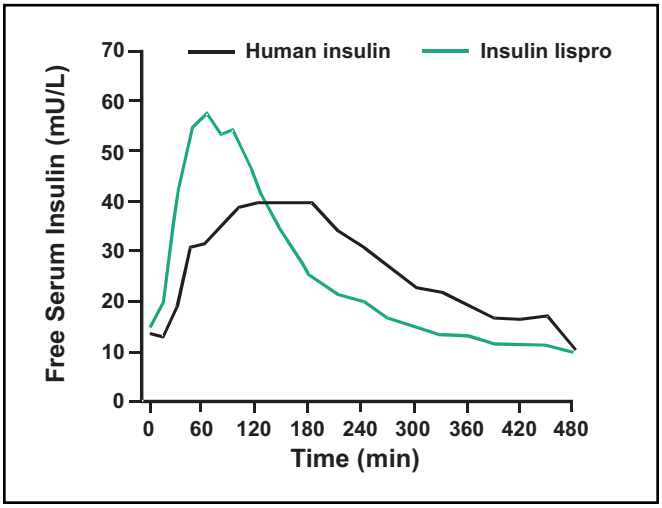

Figure 7. Serum Levels of Insulin Lispro or Regular Human Insulin Following Subcutaneous Injection.
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A clinical trial conducted in patients with type 1 diabetes demonstrated that the pharmacokinetics of insulin lispro and insulin aspart were essentially similar (Figure 8).[25]

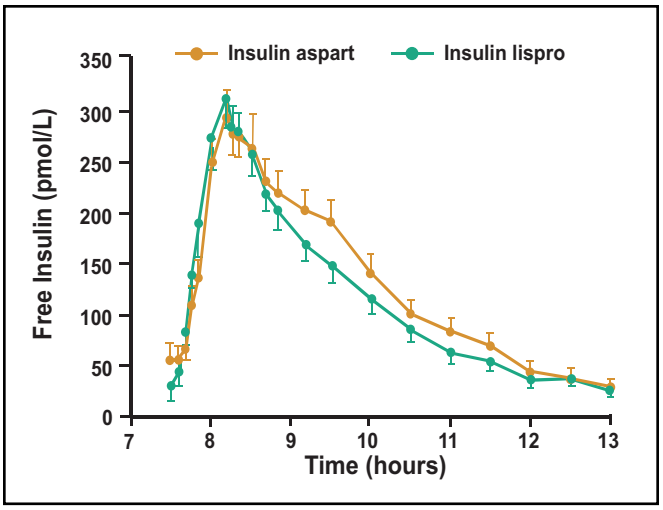

Figure 8. Comparison of Pharmacokinetics of Rapid-Acting Analogs Insulin Lispro and Insulin Aspart.
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Another similar trial showed that insulin lispro and insulin glulisine had similar pharmacokinetic and pharmacodynamic properties.[26] A brief summary of the pharmacodynamic variables (time to onset of action, time to peak action, duration of action) of rapid-acting insulin analogs is presented in Table 1.

Long-Acting Insulin Analogs

Clinical trials have indicated that the pharmacokinetic and pharmacodynamic profiles of both insulin glargine[31] and insulin detemir[22] showed distinct advantages over NPH for use as a basal insulin.

A crossover clinical trial in patients with type 1 diabetes compared the pharmacokinetics of insulin glargine, NPH insulin, and insulin Ultralente®.[32] NPH insulin peak circulating levels occurred at 4.5 hours, whereas Ultralente peak circulating levels occurred at 10.1 hours (Figure 9). Insulin glargine, however, showed a profile of low sustained circulating levels which was relatively "peakless," having a duration of action of about 22 hours.

The onset of glucose-lowering activity with insulin detemir is significantly slower with no pronounced peak compared to NPH insulin.[22] In a euglycemic clamp study of patients with type 1 diabetes, significantly less intrasubject variability in pharmacokinetic (serum insulin levels) and pharmacodynamic (glucose infusion rate) end points was found in individuals administered insulin detemir compared with either insulin glargine or NPH insulin.[33]

Table 1. Time-Action Profiles of Insulin Analogs and Premixed Insulin Analogs Currently Available in the United States

Formulation of Action (hr)	Time to Onset Action (hr)	Time of Peak Action (hr)	Duration of Action (hr)
Rapid-Acting Analogs			
Insulin lispro (Humalog®)	0.25-0.5[27]	0.8-4.3[17]	4-6[27]
Insulin aspart (NovoLog®)	<0.5[28]	1-3[18]	3-5[18]
Long-Acting Analogs			
Insulin glargine (Lantus®)	1[21]	Peakless[21]	10.8->24[21]
Premixed Insulin Analogs			
Insulin lispro 75/25 (Humalog® Mix75/25™)	<0.5[29]	1-6.5[29]	~22[29]
Insulin aspart 70/30 (NovoLog® Mix 70/30)	<0.5[30]	1-4[30]	≤24[30]

Wide interindividual variation in time to onset of action, time to peak action, and duration of action can occur. Data for insulin glulisine and insulin detemir are not available.

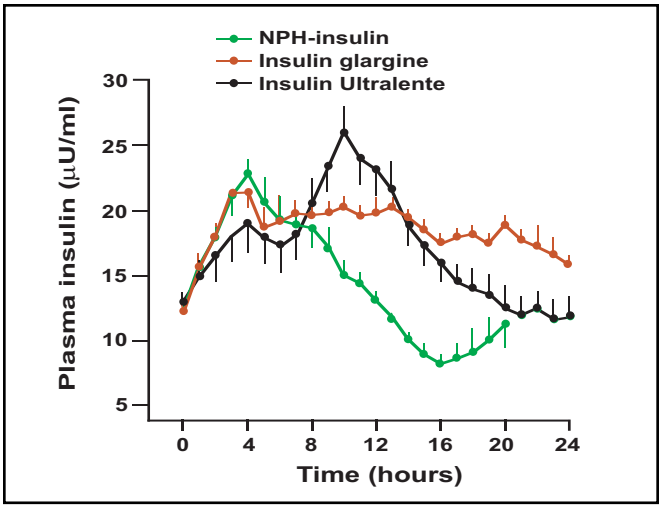

Figure 9. Pharmacokinetics of Insulin Glargine, NPH-Insulin, and Insulin Ultralente: Patients with Type 1 Diabetes.
Copyright © 2000 American Diabetes Association.
Adapted from Lepore M et al. *Diabetes.* 2000;49:2142-2148.[32]
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Premixed Insulin Analogs

Adding a Longer-Acting Component to Rapid-Acting Insulin Products

Premixed insulin formulations provide a convenient approach to cover both basal and prandial insulin requirements in one injection.[34] Newer premixed formulations include a rapid-acting insulin analog for prandial coverage and its protaminated counterpart for basal coverage. Thus, one injection has both a rapid- and intermediate-acting insulin analog.

The rationale for development of premixed insulin analogs is to try to mimic prandial and basal insulin release with one injection instead of having to manually mix a rapid-acting insulin with an intermediate-acting insulin. The advantage of using insulin analogs in premixed formulations resides in the rapid component which results in better postprandial coverage when compared to human insulin. Once- or twice-daily injections of a premixed insulin analog is a simpler regimen for many patients, reduces dosing mistakes compared to mixing two different insulin formulations in a syringe by the patient, and leads to better compliance, particularly in the elderly.

Similar to previous premixed insulin products, the premixed insulin analogs are suspensions which require the typical care to ensure that proper resuspension occurs before injecting. Vials or pens should be rolled at least 10 times before using.

Insulin Lispro 75/25

Insulin lispro 75/25 (Humalog® Mix75/25™) (75% insulin lispro protamine suspension and 25% insulin lispro injection [rDNA origin]) is a formulation consisting of 25% free insulin lispro and 75% protaminated insulin lispro.[29]

Insulin Aspart 70/30

Insulin aspart 70/30 (NovoLog® Mix 70/30) (70% insulin aspart protamine suspension and 30% insulin aspart injection [rDNA origin]) contains 30% free insulin aspart and 70% protamine insulin aspart.[30] It is important not to confuse this product with Novolin® 70/30, which is a mixture of 30% human regular insulin and 70% NPH human insulin.

Pharmacokinetic and Pharmacodynamic Studies of Premixed Insulin Analogs

In a clinical trial in patients with type 2 diabetes (previously achieving glycemic control taking twice-daily injections of human insulin 70/30), patients injected either insulin aspart 70/30 or human insulin 70/30 twice daily, immediately before breakfast and dinner.[35] As shown in Figure 10, maximal serum levels of insulin aspart were 18% higher after dinner (P <0.05), and 35% higher after breakfast the following morning (P <0.05) as compared to human insulin.

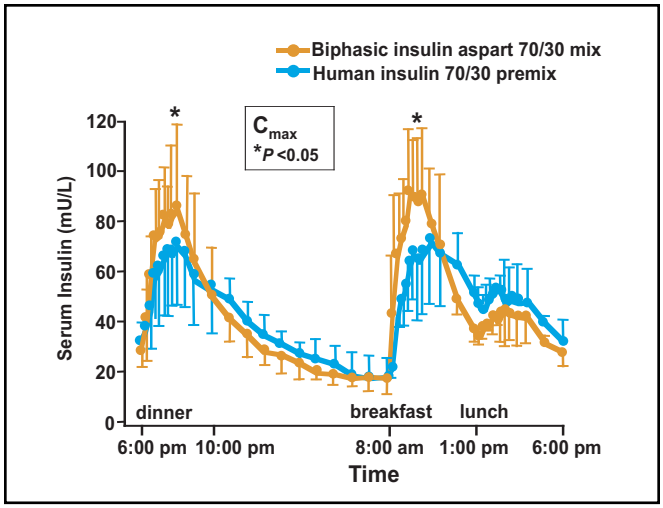

Figure 10. Pharmacokinetics of Insulin Aspart 70/30 versus Human Insulin 70/30 in Type 2 Diabetes.
Asterisks denote significant differences in maximal levels of insulin achieved (C_{max}).
Adapted from McSorly PT et al. *Clin Ther.* 2002;24:530-539.[35]

Insulin lispro 75/25 shows similar pharmacokinetic properties to the insulin aspart 70/30 mix.[33] Compared with the human insulin premixed products (such as Novolin 70/30 or Humulin 70/30), the premixed insulin analogs provide better postprandial coverage and less hypoglycemic tendencies between meals. Reduced postprandial hyperglycemia and fewer episodes of hypoglycemia have been reported for both premixed insulin analogs.

The pharmacodynamic variables of time to onset of action, time of peak action, and duration of action for insulin aspart 70/30 and insulin lispro 75/25 are summarized in Table 1.

Efficacy and Safety of Insulin Analogs

Rapid-Acting Insulin Analogs

Clinical trials of rapid-acting insulin analogs have shown improved postprandial glucose control for all three rapid-acting analogs in patients with either type 1 or type 2 diabetes. In a 6-month study of patients with type 1 diabetes, injection of insulin lispro immediately before meals was compared to regular human insulin administered 30 to 45 minutes before meals, as part of a basal-bolus regimen.[36] The basal insulin formulation of this study was either NPH or Ultralente insulin. This clinical trial demonstrated that mealtime administration of this rapid-acting insulin analog was associated with a smaller increase in postprandial plasma glucose levels than observed with regular human insulin (Figure 11). This difference was sustained during 3 months of treatment.

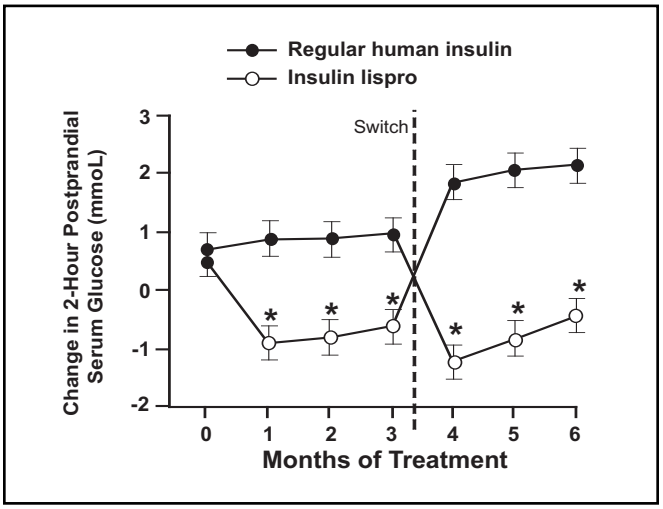

Figure 11. Postprandial Glucose Increases During Use of Insulin Lispro versus Regular Human Insulin in Type 1 Diabetes.
Asterisks: increases in 2-hour postprandial glucose were significantly less for insulin lispro treatment than regular human insulin.

Adapted from Anderson J. *Diabetes.*[46] 1997;46:265-270.[36]
Reprinted with permission from the American Diabetes Association.

In another study, men with type 1 diabetes received either insulin aspart or regular human insulin immediately before meals for 4 weeks, with NPH insulin administered at bedtime as basal therapy.[37] Detailed serum insulin and glucose profiles were collected during 24-hour sampling periods. These data indicated that during daytime periods, maximum plasma glucose concentrations

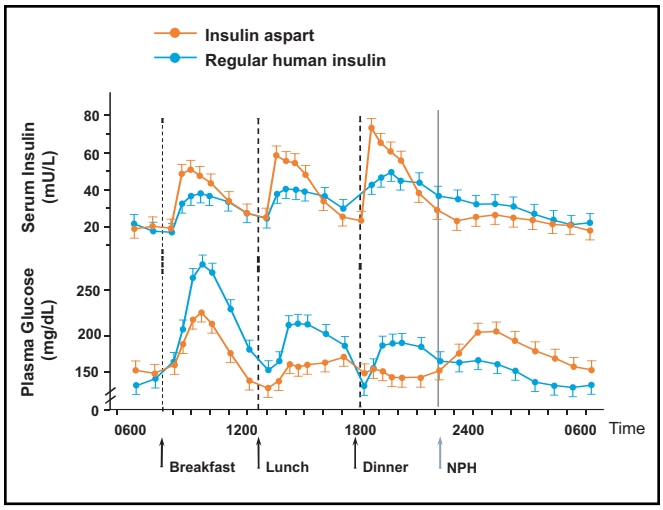

Figure 12. Insulin and Glucose Levels During Basal/Bolus Therapy of Type 1 Diabetes with Insulin Aspart or Regular Human Insulin.

From Home P. *Diabetes Care.* 1998; 21:1904-1909.[37]

were significantly lower (P <0.0001 for each period) with the insulin aspart/NPH regimen than with the regular human insulin/NPH regimen (Figure 12).

Treatment with either rapid-acting insulin analog in these two studies also resulted in fewer hypoglycemic events, particularly nocturnal hypoglycemia. More prolonged treatment with rapid-acting insulin analogs (periods up to 1 year) has been studied in other similar clinical trials. Both insulin lispro and insulin aspart have demonstrated overall glycemic control that is comparable to that of mealtime regular human insulin, as measured by final A1C values. Clinical trials in patients with type 2 diabetes have likewise demonstrated that all three rapid-acting insulin analogs are comparable to regular human insulin in terms of the long-term control of A1C values.

In contrast to insulin lispro and insulin aspart, fewer studies are available on insulin glulisine. In a study of patients with type 1 diabetes randomized to either insulin glulisine or insulin lispro in combination with insulin glargine, both rapid-acting analogs reduced postprandial glucose excursions and A1C by similar amounts; the rate of hypoglycemic events was also similar between treatments.[38] In a similar trial of patients with well-controlled type 2 diabetes, insulin glulisine + NPH provided small improvements in postprandial glucose excursions and A1C but similar rates of hypoglycemia compared with regular human insulin + NPH.[39]

The long-term consequences of improved postprandial glycemic control while achieving comparable A1C control are not currently known, but evidence such as the DECODE study[13] would imply that postprandial blood glucose control may also have cardiovascular benefits.

Long-Acting Insulin Analogs

In general, clinical trials in patients with either type 1 or type 2 diabetes have demonstrated that basal insulin glargine is associated with overall glycemic control comparable to that of basal NPH insulin, as measured in terms of reductions of A1C values, but a lower incidence of hypoglycemia, particularly nocturnal.[31]

A clinical trial compared the efficacy of once-a-day insulin glargine to that of NPH insulin (once or twice daily) in patients with type 1 diabetes, in a regimen that included mealtime insulin lispro.[40] More patients in the glargine group than in the NPH group (30% vs 17%) achieved target FPG levels (below 119 mg/dL). However, at the end of the 16-week study, reductions of A1C values in the glargine and NPH groups were comparable. Insulin glargine treatment showed significantly less variability in FPG levels than NPH insulin, although the incidence of hypoglycemia in this study was comparable for the two treatment groups. In this clinical trial, weight gain was significantly less with the use of basal insulin glargine (0.12 kg) than for basal NPH insulin (0.54 kg).

In the "treat-to-target" trial, overweight patients with inadequately controlled type 2 diabetes who were taking 1 or 2 oral antidiabetic drugs (OADs) were randomized to either insulin glargine or NPH insulin once daily.[41] The insulin dose was titrated to achieve an FPG of ≤100 mg/dL. Although about 60% of the patients reached an A1C <7% on either insulin regimen, the incidence of symptomatic hypoglycemia and nocturnal hypoglycemia was 21% to 48% lower with insulin glargine. Weight gain was similar (~3 kg) in both groups.

In another trial of patients with type 1 diabetes taking insulin aspart as the prandial insulin, insulin detemir twice daily produced greater reductions in FPG and hypoglycemia, particularly nocturnal hypoglycemia, when compared to NPH. Interestingly, no weight gain occurred in patients treated with insulin detemir.[42] In a therapeutic study of patients with type 1 diabetes,

A1C levels were 0.22% lower, whereas risk of overall and nocturnal hypoglycemia was 21% and 55% lower in patients treated with insulin detemir and insulin aspart compared to NPH and regular human insulin; weight gain was 1 kg lower in patients treated with the insulin detemir regimen.[43]

Either insulin detemir + insulin aspart, or NPH + regular human insulin were given to patients with type 2 diabetes in another study.[45] Reductions in A1C were similar but patients treated with the analog regimen experienced less day-to-day variation in FPG and lower weight gain. Although the risk of nocturnal hypoglycemia was 38% lower with the analog regimen, this did not reach statistical signifigance ($P = 0.14$).

Premixed Insulin Analogs

Efficacy and safety of premixed insulin analogs have been assessed in patients with either type 1 or type 2 diabetes. In general, premixed insulin analogs have been reported to produce overall glycemic control (A1C values) comparable to treatment with human insulin 70/30. However, clinical studies have reported improvements in postprandial glucose control using the premixed insulin analogs, and patients were able to achieve such results with the convenience of injecting immediately before meals rather than 30 minutes before mealtime (as is recommended with human insulin 70/30).

An interesting study compared the efficacy and safety of insulin lispro 75/25 to that of human insulin 70/30 in patients with type 2 diabetes.[44] Each premixed insulin analog was administered twice daily for 3 months, before breakfast and before dinner. The median time that elapsed from injection to mealtime was 3 minutes for insulin lispro 75/25, and 28 minutes for human insulin 70/30. At the end of the study, overall glycemic control was similar for insulin lispro 75/25 mix and human insulin 70/30 (7.8% vs 8.1%). However, 2-hour postprandial glucose levels (patient self-monitored) after breakfast or dinner were significantly lower for insulin lispro 75/25 (167 mg/dL vs 185 mg/dL).

Postprandial glycemic control with insulin aspart 70/30 was compared to that of human insulin 70/30 in a randomized crossover trial in patients with type 1 diabetes.[45] On 3 separate days, treatments were: insulin aspart 70/30 injected immediately before, human insulin 70/30 injected immediately before, or human insulin 70/30 injected 30 minutes before a standard breakfast. Insulin aspart 70/30 therapy resulted in significantly lower postprandial glucose levels than human insulin 70/30, whether human insulin 70/30 was injected immediately before or 30 minutes before breakfast. Postprandial glucose was 23% lower with the premixed insulin analog than with human insulin 70/30 administered just before breakfast, and 9% lower than human insulin 70/30 administered 30 minutes before breakfast.

Treatment of either type 1 or type 2 patients with insulin aspart 70/30 was further assessed in another clinical trial.[46] All patients received either insulin aspart 70/30 within 10 minutes before breakfast and dinner, or human insulin 70/30 injected 30 minutes before breakfast and dinner. At the end of treatment, A1C values of the two groups differed by only 0.01%. However, the mealtime increases in blood glucose were significantly lower for insulin aspart 70/30 (by 12 mg/dL) than human insulin 70/30. The incidence of hypoglycemic episodes did not appear to be different between the two treatment groups.

In two trials in which patients were treated to target for A1C, larger reductions in A1C levels occurred with premixed insulin analogs compared to insulin glargine. In insulin-naive patients with poorly controlled type 2 diabetes who remained on metformin, with or without pioglitazone, 66% of patients treated with insulin aspart 70/30 twice daily for 28 weeks achieved an A1C <7% compared to only 40% treated with insulin glargine; 42% reached an A1C ≤6.5% with insulin aspart 70/30 compared to 28% with insulin glargine.[47] With insulin aspart 70/30, postprandial glucose excursions were 40% and 55% lower after breakfast and dinner compared with insulin glargine. Although no subjects treated with insulin aspart 70/30 experienced severe hypoglycemia, the frequency of minor hypoglycemia was greater than in those using insulin glargine.[47] Treatment satisfaction was similar in the two groups.[47]

In a similar trial of patients with type 2 diabetes starting insulin therapy but remaining on metformin, 41% treated with insulin lispro 75/25 twice daily reached an A1C <7% compared to 22% treated once daily with insulin glargine;[48] With insulin lispro 75/25, postprandial glucose excursions after breakfast and dinner were 60% and 65% lower, but the rates of hypoglycemia were significantly higher compared with insulin glargine.[48]

Another trial with patients inadequately controlled on once- or twice-daily insulin, alone or in combination with OADs, showed that insulin lispro 75/25 twice daily lowered A1C by an additional 0.6% compared to insulin glargine once daily.[49] Overall, glucose excursions were 25% lower with insulin lispro 75/25, although while the rate of hypoglycemia was not different between treatments. No major hypoglycemic event occurred in either trial.[48,49]

Patient Subgroups: Use of Insulin Analogs in Clinical Practice

Selection Factors: The Appropriate Insulin Regimen

A wide range of available insulin formulations can make it a challenge to choose the right treatment for each patient. However, such a wide range of choices offers many possibilities for tailoring therapy to the clinical and psychological needs of the individual patient. The choice of an appropriate treatment should be made after weighing an individual patient's daily clinical needs, such as:

- Patient's level of intelligence and diabetes education
- Overall glycemic control with previous regimen (last A1C determinations)
- Blood glucose monitoring practice, understanding of the results, and capacity to make therapeutic changes accordingly
- Patient's comprehension of the need to use insulin and degree of commitment to the new treatment (determines if a more or less intensive insulin program can be initiated)
- Flexibility and willingness to increase number of injections to achieve glycemic control
- Adherence to current regimen and lifestyle factors
- Mixing habits: Is the patient routinely mixing insulin formulations before injection?
- Optimal glycemic control when convenience dictates routine: Does the patient typically inject insulin just before meals, rather than planning injections 30 minutes before?
- Special modes of insulin delivery: Is the patient a candidate for use of a continuous subcutaneous insulin infusion pump? Does the patient have need of an insulin pen, or a device with 1/2-unit increments?
- Difficulties with previous insulin regimens
- Vision and dexterity problems
- Special problems (eg, high risk of nocturnal hypoglycemia, coronary heart disease, tendency to fall or become confused, erratic physical activity habits, and job-related needs)

Rapid-Acting Insulin Analogs

In clinical trials, it has repeatedly been demonstrated that rapid-acting insulin analogs produce better postprandial glucose control than regular human insulin.[17] Use of a rapid-acting analog (insulin lispro or insulin aspart) is therefore a tactic for improving post-prandial glycemic control in patients who want the convenience and flexibility of injecting their bolus insulin immediately before meals. Insulin lispro is available in vials and a disposable pen (Humalog®Pen); insulin aspart is available in vials, in cartridges for durable devices (NovoPen®3, NovoPen®Junior, InDuo®, Innovo®), and in a disposable pen (FlexPen®).[50]

A rapid-acting insulin analog may prove of particular value in patients who have been previously poorly controlled, particularly in the postprandial state, and have wide glycemic fluctuations with frequent hypoglycemic episodes. The improved reproducibility of rapid-acting insulin analogs means that improvements of glycemic control may be obtained with less day-to-day variation, less changes and corrections in insulin doses, and more reassurance for the patient.

For patients deemed suitable for intensive therapy using continuous subcutaneous insulin infusion pumps, it is necessary to use a soluble insulin formulation that acts as rapidly as possible. A rapid-acting insulin analog therefore has advantages over regular human insulin for use in continuous subcutaneous infusion therapy. In the United States, the only insulin formulations currently approved for use in subcutaneous insulin infusion pumps are insulin aspart (NovoLog), insulin lispro (Humalog), and insulin glulisine (Apidra). In a clinical trial of patients with type 2 diabetes, continuous subcutaneous insulin infusion with insulin aspart was as effective as a regimen of multiple daily injections of bolus insulin aspart with NPH insulin as a basal insulin.[51] However, patient satisfaction measures conducted during this study indicated that patients preferred the pump over their previous regimen, because of the convenience and flexibility of pump therapy.[51]

When patients wish to mix insulin formulations, insulin aspart or insulin lispro may be mixed with NPH insulin before injection (the insulin analog should be drawn

into the syringe first), and the mixture should be injected immediately.[17,18] Mixing of insulin lispro with Humulin® U (Ultralente human insulin zinc suspension) has also been tested with satisfactory results, when mixing is immediately followed by injection. Mixing of insulin aspart with formulations other than NPH insulin has not been studied. The advantage of self-mixing is that the patients may increase or decrease the dose or proportions of each type of insulin according to the premeal BG level, the size and type of meal including carbohydrate counting, and the level of exercise they undertake. On the other hand, it increases the complexity of the treatment, the possibility of errors, and the learning required by the patient.

Long-Acting Insulin Analogs

Long-acting insulin analogs are intended for use as basal insulin with minimal peaks in activity. Appropriate candidates for a long-acting insulin analog include patients who have repeatedly experienced hypoglycemic episodes during therapy with NPH insulin as the basal therapy. Both insulin glargine and insulin detemir can prove particularly helpful in minimizing nocturnal hypoglycemia since both of these long-acting insulin analogs reduce the likelihood of unpredictably high insulin levels during the night.

A long-acting insulin analog can also prove very helpful in patients with type 2 diabetes who have some insulin secretory capacity (early in the course of their disease) where a steady baseline level of insulin throughout the day may be enough to decrease the A1C levels to goal (approximately 50% of patients). This basal insulin supply can be further supplemented by OADs in some patients with type 2 diabetes. However, this basal-only regimen may not provide sufficient coverage of the postprandial glucose excursions. Addition of a rapid-acting insulin analog or switching to a premixed insulin analog are options when this occurs.

Premixed Insulin Analogs

Premixed insulin analogs provide a simple treatment option for patients with type 2 diabetes at the beginning of insulin therapy and throughout the progression of the disease with only one type of insulin formulation. Premixed insulin analogs may be used in programs of one, two, or three injections a day according to the pathogenic state of the diabetes, and to the mealtimes of the patient. In the initial stages of insulin therapy in patients with OAD failure, one injection of a premixed insulin analog before supper may be all that is necessary to attain therapeutic goals.[52] Premixed analogs can also be helpful for patients who do not require a very intensive therapeutic regimen, but need both postprandial and between-meal glycemic control. Twice-daily injections of premixed insulin analogs may be appropriate in such patients. In patients who require and accept more intensive control, and have large or late lunches or very late dinners, a therapeutic program of three injections of the premixed insulin analogs gets results very close to a basal-bolus program of multiple insulin injections.[52] Insulin aspart 70/30 is available in vials and in a prefilled disposable pen (NovoLog Mix 70/30 FlexPen®); insulin lispro 75/25 is also available in vials and in a disposable pen (Humalog®Mix75/25 Pen).

In addition, not every patient with type 1 diabetes can be optimally managed with a program of intensive insulin therapy using basal-bolus injections. For a patient new to insulin therapy, compliance may be more likely with a simpler insulin injection regimen. In such patients, a twice-daily regimen of a premixed insulin analog provides coverage of at least two mealtime glucose loads (if sufficient time is allowed between daily injections), while providing some sustained insulin coverage. Premixed insulin analogs have the advantage that they can be injected immediately before meals, which may result in improved compliance and better postprandial glycemic control.

Summary

The insulin analogs and premixed insulin analogs currently available represent advances of biotechnology not only to produce insulin but to improve upon the fundamental time-action properties of insulin. Insulin analogs have been produced by modifying the native amino acid sequence of human insulin, and for insulin detemir, adding a C14 fatty acid moiety that enables it to bind to albumin. The range of options includes rapid-acting insulin analogs instead of mealtime regular human insulin products, long-acting insulin analogs instead of crystalline preparations of insulin such as NPH insulin and insulin Ultralente, and premixed insulin analogs that are alternatives to the use of regular human insulin/NPH insulin mixtures. Insulin analogs and premixed insulin analogs mimic physiological secretion of insulin at mealtimes and the steady basal secretion of insulin between meals more closely than human insulins. Additional features include better reproducibility of insulin action from injection to injection, and reduced incidence of hypoglycemia (especially at night). With their more physiological time-action profiles, insulin analogs and premixed insulin analogs represent a significant advance for the pursuit of optimal glycemic control for patients.

Case Study Example: Clinical Use of Insulin Analogs

Mrs. G is a 55-year-old Hispanic woman with type 2 diabetes who was referred to a diabetes educator by her primary care physician for insulin initiation and diabetes self-management training. Mrs. G has resisted initiation of insulin for the past 2 years because of fears related to complications family members have suffered which she associates with insulin therapy. Her A1C values remained over 13% on maximum doses of a sulfonylurea and metformin. She was not monitoring her blood glucose levels, but a random blood glucose check showed a level of 340 mg/dL. A review of physical systems demonstrated polyuria, polydipsia, blurred vision, and lower extremity paresthesias. Mrs. G has a family history of type 2 diabetes, hypertension, and cardiovascular disease. Her current medications include: metformin 850 mg PO TID; glimepiride 4.0 mg PO BID; lisinopril 20 mg PO QD; atorvastatin 40 mg PO QD. She weighs 180 lbs and is 5'3" tall (BMI value of 32 kg/m^2). Her blood pressure is 140/85 mm Hg. Other laboratory values were as follows: Spot urine microalbumin testing, 120 mg/g; total cholesterol, 190 mg/dL; HDL, 40 mg/dL; LDL, 110 mg/dL; triglycerides, 200 mg/dL.

Mrs. G met with a diabetes educator for education on diabetes self-management skills and to explore her resistance to initiating insulin therapy. They discussed Mrs. G's fears and family history. The diabetes educator was able to dispel many of the myths Mrs. G believed regarding insulin therapy. After discussing her concern about injections and insulin therapy, Mrs. G decided to try a premixed insulin analog twice daily (half of the total daily dose just before breakfast and half just before dinner) in a prefilled insulin pen. The diabetes educator pointed out that this regimen could control both the postprandial and basal glucose excursions in one injection. Metformin was retained and the sulfonylurea was discontinued. Mrs. G agreed to self-monitor her blood glucose twice daily in the morning before breakfast and 2 hours after each meal, alternating between dinner and lunch every 3 days. She also consulted a dietitian for medical nutrition therapy, targeting a 5% to 7% weight loss and to explore opportunities for increased physical activity. They also discussed ways Mrs. G could incorporate her family's favorite ethnic foods into her meal plan and how to reduce her protein intake to control the albuminurea.

After 6 months, Mrs. G's FPG had decreased to 106 mg/dL and her PPG readings were usually less than 140 mg/dL. Her A1C had decreased to 6.9% and she had lost 22 lbs. She is making better food choices and is now exercising for 30 minutes three times a week. She has learned how to successfully modify her family's favorite recipes for inclusion in her meal plan and feels confident that she will be able to continue to successfully manage her diabetes while taking care of her family.

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Post-test

Rationale for the Development and Clinical Use of Insulin Analogs and Premixed Insulin Analogs

This program can also be completed online at www.MedEdToday.com. Please provide one answer for each question (11 or more correct answers are necessary for successful completion). Place all answers on the separate answer sheet provided on the program evaluation form that follows this post-test.

1) **Compared with human insulin formulations, insulin analogs and premixed insulin analogs have _____.**
   A. More physiological time-action profiles
   B. Provide more convenient dosing options
   C. Both A & B
   D. Can all be mixed with other insulin formulations

2) **All of the following are rapid-acting insulin analogs EXCEPT _____.**
   A. Insulin aspart
   B. Insulin glargine
   C. Insulin glulisine
   D. Insulin lispro

3) **The time to onset of action of rapid-acting insulin analogs is _____ than regular human insulin.**
   A. Faster
   B. Slower
   C. Not different

4) **What changes have occurred by alterations in human insulin to achieve rapid-acting insulin analogs?**
   A. No alterations were made.
   B. The pH of rapid-acting analogs has changed.
   C. There is a reduced tendency to associate into molecular hexamers.
   D. The concentration of insulin product has changed.

5) **Which property characterizes insulin glargine as different from NPH insulin or Ultralente?**
   A. There is no visible difference from NPH insulin; it is indistinguishable.
   B. Insulin glargine is a clear solution, not a cloudy suspension like NPH insulin or Ultralente.
   C. Insulin glargine has a very basic pH, over 9.
   D. Insulin glargine can be mixed with other insulin formulations if injected immediately.

6) **What is the basic composition of insulin analog mixture products such as Humalog Mix75/25 and NovoLog Mix 70/30?**
   A. There is a portion that is rapid-acting insulin analog – the rest is insulin glargine.
   B. There is a portion that is rapid-acting insulin analog – the rest is regular human insulin.
   C. There is a portion that is rapid-acting insulin analog – the rest is zinc-based.
   D. There is a portion that is rapid-acting insulin analog – the rest is a sustained-action, protaminated form of the rapid-acting insulin analog.

7) **Which of the following answers best describes the unique properties of rapid-acting insulin analogs (insulin lispro, insulin aspart, insulin glulisine) as compared to regular human insulin?**
   A. Rapid-acting insulin analogs are used for day-long basal coverage, whereas regular human insulin is no longer effective after 8 hours.
   B. Rapid-acting insulin analogs can be injected immediately before meals, with glycemic control results at least as acceptable as regular human insulin injected 30 minutes before the meal.
   C. Rapid-acting insulin analogs can be injected 2 hours after the meal and no difference can be demonstrated from injection of regular human insulin 30 minutes before a meal.
   D. Rapid-acting insulin analogs cannot be used in a basal/bolus regimen.

8) **Which insulin analog has a C14 fatty acid moiety (myristic acid) on the B-chain lysine residue at B29?**
   A. Insulin glargine
   B. Insulin aspart
   C. Insulin detemir
   D. Insulin lispro

9) **Insulin aspart is made by insertion of a plasmid into _____.**
   A. *Escherichia coli*
   B. A proinsulin molecule
   C. *Saccharomyces cerevisiae*
   D. None of the above

10) **Which mode of administration is not an appropriate use of rapid-acting insulin analogs (insulin lispro, insulin aspart, or insulin glulisine)?**
   A. Continuous subcutaneous insulin infusion (pump) therapy
   B. Mixing with NPH-insulin just before injection
   C. Once-a-day use as a basal insulin
   D. Mealtime use as the bolus insulin of a basal/bolus regimen

11) **Clinical trials with rapid-acting insulin analogs have shown _____.**
   A. Lower postprandial glucose levels than with regular human insulin
   B. Lower risk of hypoglycemic events than with regular human insulin
   C. A1C values comparable to regular human insulin
   D. All of the above

12) **Which insulin would most likely provide the best postprandial blood glucose control if each was injected immediately before a meal?**
   A. Insulin glargine
   B. Insulin aspart
   C. Human insulin 70/30
   D. Regular human insulin

13) **A patient on a basal insulin regimen has an A1C level of 8.4% and is experiencing postprandial glucose excursions. Which of the following regimens would minimize the number of injections while providing basal, as well as some postprandial, coverage?**
   A. Regular human insulin, injected at random times when the patient felt he was hyperglycemic
   B. Insulin lispro before every meal
   C. Insulin aspart 70/30 mix or insulin lispro mix 75/25, prior to breakfast and prior to dinner
   D. NPH insulin 3 times a day

14) **Sound evidence of the advantages of mealtime rapid-acting insulin analogs over mealtime regular human insulin has been demonstrated because _____.**
   A. Postprandial glycemic control is improved
   B. Injections of daily basal insulin can be discontinued after starting rapid-acting analogs
   C. Mealtime regular human insulin stops working after prolonged treatment, but insulin analogs do not
   D. Patients do not like to inject just prior to eating

Program Evaluation (069-999-05-214-H01)

Rationale for the Development and Clinical Use of Insulin Analogs and Premixed Insulin Analogs

DIRECTIONS: Please rate each of the following on a scale of 1 to 5
5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor

Extent That Program Activities Met the Identified Objectives

After reading this monograph, were you able to:

	Outstanding				Poor
Explain the rationale for the development of insulin analogs	5	4	3	2	1
Describe the molecular alterations of rapid- and long-acting insulin analogs	5	4	3	2	1
State the major differences between the time-action profiles of insulin analogs and human insulins	5	4	3	2	1
Describe how insulin analogs are manufactured	5	4	3	2	1
Identify major considerations when individualizing treatment with insulin analogs	5	4	3	2	1

Overall Effectiveness of the Activity

Objectives were related to overall purpose/goal of activity	5	4	3	2	1
Relates to my practice needs	5	4	3	2	1
Will help me improve patient care	5	4	3	2	1
Stimulated my intellectual curiosity	5	4	3	2	1
Overall quality of material	5	4	3	2	1
Activity met my expectations	5	4	3	2	1
Avoided commercial bias or influence	5	4	3	2	1

Will the information presented change your practice? _____Yes _____No

If yes, please describe any change(s) you plan to make in your practice as a result of this program.

If no, is it because you already practice this way? _____Yes _____No

	Very Committed				Not at all Committed
How committed are you to making these changes?	5	4	3	2	1

Additional comments about this educational activity?

Please list any other topics that would be of interest to you for future educational activities.

Post-test Answer Key

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

8 ☐ 9 ☐ 10 ☐ 11 ☐ 12 ☐ 13 ☐ 14 ☐

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