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Advances in diabetes therapy: Rapid- and long-acting insulin analogs

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Advances in diabetes therapy: Rapid- and long-acting insulin analogs

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The desired goal of treatment for diabetes is to model the natural timing of insulin secretion and action as closely as possible.

Achieving normoglycemic balance is complicated, and varies significantly from patient to patient. New insulin agents for the treatment of diabetes continue to be developed, and with each technological advance, new benefits are realized.

During the past decade, research focused on achieving this goal. Insulin analogs are synthetically manufactured by making amino-acid modifications to human insulin. The result is a product that's better able to replicate the time course action profile of normal physiologic insulin secretion.

Physiologic insulin replacement

A discussion of the body's normal pattern of insulin secretion will assist in understanding the role of insulin analogs in diabetes management. Figure 1 shows the physiologic insulin secretion pattern in a healthy individual over a 24-hour period that included three standard meals. The large peaks of insulin secretion corresponding to each meal is called bolus or mealtime insulin secretion. This endogenous insulin secretion, which is a response to the meal stimulus, limits hyperglycemia after a meal through a rapid release of insulin with an immediate rise in concentration, reaching peak effect



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GOAL

To assist pharmacists in caring for diabetes patients and help them determine the proper processes on which to counsel specific patients

CREDIT

This lesson provides two hours of CE credit and requires a passing grade of 70%.*

OBJECTIVES

Upon completion of this article, the pharmacist should be able to:

- ✓ Explain the normal physiology of insulin secretion and action in a person who does not have diabetes
- ✓ Explain the pharmacokinetic/pharmacodynamic differences of the insulin analogs compared with traditional short-, intermediate-, and long-acting insulins
- ✓ Recommend the appropriate dose of an insulin analog when converting a patient from NPH or regular human insulin
- ✓ Provide patient counseling regarding proper insulin analog administration and storage
- ✓ Discuss available insulin delivery systems for use with insulin analogs

*To receive credit you must score 70% or higher on the quiz and complete the evaluation. Upon successful completion, the University of Florida College of Pharmacy will mail Statements of Credit for written quizzes within 10 working days. Participants completing the program on-line may print a Statement of Credit after successfully completing the program.

in approximately one hour. However, it has a relatively short duration of action, as it wanes over the course of two to three hours. Bolus insulin secretion accounts for approximately one-half of the body's total daily insulin secretion.

A constant secretion of insulin that is not related to food intake also occurs over a 24-hour period. This basal or background insulin secretion occurs at a relatively constant rate with no pronounced peak effect. Basal insulin is responsible for suppressing glucose production between meals and overnight by regulating glucose output from the liver. In general, basal insulin secretion makes up the remaining 50% of the body's total daily insulin secretion; however, these proportions may vary according to the eating habits of the individual. When designing insulin replacement regimens, the term *basal/bolus* is often used to describe a method of insulin delivery that mimics very closely what takes place inside the body. It typically consists of four injections of insulin: three injections of rapid-acting or mealtime insulin, corresponding with meals, and one injection of long-acting or basal insulin. This balance provides the patient with the correct amount of insulin when needed in order to attain normoglycemia. Frequent blood glucose monitoring is required, and referral to a diabetes educator or another qualified healthcare professional is recommended in order to properly determine mealtime insulin doses.

Limitations of conventional insulin products and new solutions

The need to develop insulin analogs was due largely to the limitations imposed by conventional insulin products and a desire to achieve better glucose control using the basal/bolus concept. Regular insulin has a slow onset of action, which requires that it be given 20 to 40 minutes before a meal. This may be inconvenient, especially when dining out or having an inconsistent meal schedule, leading to poorly timed doses and/or omitted doses. Administering regular insulin just prior to or after a meal may

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result in elevated postprandial glucose levels. Furthermore, regular insulin has approximately a six- to eight-hour duration of action and a peak effect that often occurs after the peak of glucose absorption, even if proper timing of the administration does occur. This in turn may increase the risk of hypoglycemia, especially in between meals.

The newer insulin analogs, aspart (NovoLog), lispro (Humalog), and glulisine (Apidra), have a faster onset and shorter duration of activity that more closely mimics the physiologic insulin released from the body. This is viewed as a major advantage, since these agents may be administered at the start of the meal or even after the meal, allowing patients greater flexibility. In addition, rapid-acting insulin analogs have a peak effect that more closely matches the peaking effect of absorbed glucose, when compared with regular insulin. This results in less hypoglycemia with multiple daily dosing.

NPH insulin also has limitations and does not mimic normal physiologic insulin secretion. The duration of action is less than 24 hours, which requires patients to receive multiple injections. NPH insulin also demonstrates a peak effect roughly six to eight hours after injection, which increases the risk of hypoglycemia, especially nocturnal hypoglycemia. Furthermore, since NPH insulin is a suspension, not a homogenous clear solution, considerable day-to-day variability in insulin action exists. This in turn can lead to patients experiencing variability in glycemic control.

The ideal characteristics of a basal insulin must mimic normal pancreatic basal insulin secretion by having a relatively smooth, peakless

Table 1
Pharmacokinetics of bolus insulin

	Onset	Peak	Duration
Intrinsic bolus insulin effect	~ 5 min	30-60 min	2.5-3 hrs
Rapid-acting	5-15 min	30-90 min	3-5 hrs
Insulin lispro (Humalog)			
Insulin aspart (NovoLog)			
Insulin glulisine (Apidra)			
Short-acting	30-60 min	2-3 hrs	5-8 hrs
Regular insulin (Humulin R/Novolin R)			

activity profile, which greatly reduces the risk of hypoglycemia. The variability in the insulins' action should be at a minimum to allow reproducible, predictable effects. Insulin glargine (Lantus) and detemir (Levemir) are long-acting insulin analogs that have properties consistent with an ideal basal insulin. Reduced hypoglycemia, predictable activity profiles, and a duration of action up to 24 hours are considered the major advantages of these

insulins.

Rapid-acting and long-acting insulin analogs have great potential to provide insulin coverage that mimics the physiologic action of naturally produced insulin. These new insulin analogs play an important role in the insulin regimen of patients with diabetes.

RAPID-ACTING INSULIN ANALOGS

Insulin lispro, introduced in 1996, was the first insulin analog. This was followed four years later by insulin aspart and, most recently, insulin glulisine. The pharmacokinetic and pharmacodynamic properties of these agents are similar and result in a faster onset of action and shorter duration of action compared with regular human insulin (RHI) (see Table 1). This change in properties is a result of alterations in the amino-acid sequence of the human insulin molecule through recombinant DNA technology.

Safety and efficacy

Clinical studies comparing each rapid-acting analog to RHI in Type 1 and Type 2 diabetes revealed improved lowering of postprandial blood

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glucose readings and less nocturnal hypoglycemia. One study found that the postprandial rise in glucose levels was lower in the insulin lispro group compared with RHI. The rates of nocturnal hypoglycemia, asymptomatic hypoglycemic episodes, and overall rate of hypoglycemia were also lower in the insulin lispro group. Similar findings were seen with insulin aspart and insulin glulisine when compared with RHI in evaluating use in Type 2 diabetes, and all three agents against RHI in Type 1 diabetes.

The pharmacokinetics of the short-acting analogs suggest that administration after a meal is consumed would result in similar lowering of postprandial glucose values. This was evaluated in 866 patients with Type 1 diabetes receiving basal insulin therapy with insulin glargine with either RHI 30 minutes prior or insulin glulisine 15 minutes prior or 15 minutes after each meal over a 12-week period. HbA_{1c} reductions and two-hour postprandial glucose values were significantly lower in the pre-meal insulin glulisine group as compared with postmeal glulisine or RHI. There were no differences in the two-hour postprandial reductions of postmeal insulin glulisine and RHI. An advantage found with postmeal administration of glulisine was a significant reduction in weight compared with the other two groups. This study reveals that postmeal administration of insulin glulisine is as efficacious as therapy with RHI. Thus, postmeal administration of glulisine, and likely insulin aspart and lispro, is therapeutically acceptable.

Dosing

Initiation of a rapid-acting insulin analog, or any insulin, is dependent on several patient factors: current blood glucose readings (fasting and postprandial), timing and carbohydrate consumption at each meal, and, most important, the patient's understanding and willingness to take injections. Standardization of starting doses is not generally recommended; however, when adjusting doses, increments of one to four units are acceptable. In Type 1 diabetes, a dose of one to two units of

insulin generally produces a 50 mg/dl glucose reduction. In Type 2 diabetes, this ratio is not as predictable due to differing degrees of insulin resistance. Therefore, patients may require higher amounts of insulin to achieve the same effect. Dosing adjustments of rapid-acting analogs are ideally based on postprandial glucose readings and the dose may be titrated every three to four days until goal glucose readings are achieved.

When changing from RHI to a rapid-acting insulin analog, a 1:1 conversion is acceptable; however, great interpatient variability exists among RHI. Monitoring the two-hour postprandial glucose is recommended to allow for proper bolus dose titration and assessment of hyper- or hypoglycemia. Monitoring the fasting blood glucose is also recommended, as improvements in postprandial blood glucose may necessitate alteration in basal insulin dose.

Administration

Rapid-acting insulin analogs are available in clear solution; therefore, rolling to mix the product is not necessary. There are several available delivery mechanisms, including vials, pens, and cartridges. Prescribing information regarding the timing of administration varies slightly among the rapid-acting insulin analogs. Insulin lispro should be injected subcutaneously 15 minutes before or immediately after a meal, insulin aspart should generally be injected within five to 10 minutes before a meal, and insulin glulisine should be administered within 15 minutes before or 20 minutes after a meal. If a scheduled meal is skipped, the dose of rapid-acting analog should be skipped as well, in order to prevent hypoglycemia. Pharmacists can assist their patients by explaining the differences in the timing of the dose when RHI is changed to a rapid-acting analog, since administering rapid-acting analogs 30 minutes or more before a meal—as patients may be accustomed to with their RHI—may result in premeal hypoglycemia.

The rapid-acting analogs may be mixed in the same syringe with

Table 2
Available insulin analogs

	Manufacturer	Year of FDA approval	Mixing compatibility	Premixes available	Storage	Retail price*
RAPID-ACTING						
Insulin lispro (Humalog)	Eli Lilly	1996	NPH	75/25 75% insulin lispro protamine 25% insulin lispro	Vial: Store unopened in refrigerator up to exp. date. Store opened up to 28 days at room temperature.	10-ml vial: \$78.47
				50/50 50% insulin lispro 50% insulin lispro protamine	Humalog: Store unopened in refrigerator up to exp. date. Store opened up to 28 days at room temperature. Do not refrigerate after opening. Humalog premix pens: Store unopened in refrigerator up to exp. date. Store opened up to 10 days at room temperature. Do not refrigerate after opening.	Humalog pen: \$152.60 for 5 pens Cartridges: \$31.19 for 5 cartridges
Insulin aspart (Novolog)	Novo Nordisk	2000	NPH	70/30 70% insulin aspart protamine 30% insulin aspart	Vial: Store unopened in refrigerator up to exp. date. Store opened up to 28 days at room temperature.	10-ml vial: \$77.47
					Pen/cartridges: Store unopened in refrigerator up to exp. date. Store opened up to 28 days at room temperature. Do not refrigerate after opening.	FlexPen: \$149.89 for 5 pens Cartridges: \$135.28 for 5 cartridges
Insulin glulisine (Apidra)	Sanofi-Aventis	2004	NPH	None available	Vial: Store unopened in refrigerator up to exp. date. Store opened up to 28 days at room temperature.	10-ml vial: \$80.86
					Cartridges: Store unopened in refrigerator up to exp. date. Store opened up to 28 days at room temperature. Do not refrigerate pen device.	Cartridges: \$162.68 for 5 cartridges

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Table 2						
Available insulin analogs (continued)						
	Manufacturer	Year of FDA approval	Mixing compatibility	Premixes available	Storage	Retail price*
LONG-ACTING						
Insulin glargine (Lantus)	Sanofi-Aventis	2000	None	None available	Vial: Store unopened in refrigerator up to exp. date. Store opened up to 28 days at room temperature.	10-ml vial: \$73.77
					Cartridges: Store unopened in refrigerator up to exp. date. Store opened up to 28 days at room temperature. Do not refrigerate pen device.	Cartridges: \$145.25 for 5 cartridges
Insulin detemir (Levemir)	Novo Nordisk	2005	None	None available	Vial: Store unopened in refrigerator up to exp. date. Store opened up to 42 days at room temperature.	10-ml vial: \$77.99
					Pen/cartridges: Store unopened in refrigerator up to exp. date. Store opened up to 42 days at room temperature. Do not refrigerate individual cartridges or pens after opening.	FlexPen: \$146.99 for 5 pens Cartridges: \$158.64 for 5 cartridges
Source: Drugstore.com, accessed June 2006						

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NPH insulin. The rapid-acting insulin analog should be drawn into the syringe first to prevent alterations in the pharmacokinetics by the protamine of the longer-acting products. Rapid- and long-acting insulin analogs should not be mixed in the same syringe and are not available together as premixed products due to instability of the solution.

Premixed products

Available premixed rapid-acting analog insulins are listed in Table 2. Premixed insulin products are suspensions that should be rolled, not shaken, 15 times in the hands for consistent mixing of the solution. Dosing of premixed rapid-acting insulin analogs should follow the prescribing information for the rapid-acting analog component, as previously discussed.

These products are traditionally dosed twice a day, which does not allow for midday or bedtime snacks. For this reason, it is preferable not to use premixed insulin in patients with Type 1 diabetes. In addition, due to the intermediate-acting component, premixed insulins should never be administered intravenously or by continuous insulin pump infusion.

Adverse reactions

Hypoglycemia is the most common adverse reaction with insulin administration. Patients are at the highest risk for hypoglycemia if a meal is delayed or skipped after the administration of a rapid-acting analog due to the fast onset of action. For patients who do not eat what they intend at a meal, predicting a premeal dose may be difficult. If only a small portion of the meal is eaten, the risk of hypoglycemia increases. These patients may benefit from postmeal injections of a rapid-acting analog dosed on carbohydrate intake.

Allergic reactions (pruritus, rash) and injection-site reactions (lipodystrophy) using rapid-acting insulin analogs are similar to those from RHI. Patients should be counseled to report any signs of a sys-

Table 3
Pharmacokinetics of basal insulin

	Onset	Peak	Duration
Intrinsic basal insulin effect	Consistent	None	24 hrs
LONG-ACTING INSULIN ANALOGS			
Insulin detemir (Levemir)	2-4 hrs	Slight 4-14 hrs	20-24 hrs
Insulin glargine (Lantus)	2-4 hrs	None	20-24 hrs
INTERMEDIATE-ACTING HUMAN INSULIN			
Isophane insulin—NPH (Humulin N/Novolin N)	2-4 hrs	4-10 hrs	10-16 hrs
Insulin zinc—Lente (Humulin L/Novolin L)	2-4 hrs	4-12 hrs	12-18 hrs
LONG-ACTING HUMAN INSULIN			
Insulin Zinc—Extended Ultralente (Humulin U)	6-10 hrs	10-16 hrs	18-24 hrs

temic or localized reaction to their physician immediately.

Use in special populations

As with RHI, a decrease in renal clearance occurs with declining renal function, resulting in increased insulin effects. An increase in circulating insulin levels was also detected in patients with hepatic impairment. Cautious dose adjustments and increased blood glucose monitoring are recommended in patients who have decreased renal or hepatic function.

Published controlled trials evaluating rapid-acting insulin analog use in pregnant or lactating mothers are limited. In a systematic review of the literature, insulin lispro showed improved blood glucose lowering in pregnant women, with no increase of congenital defects. Studies of pregnant women with diabetes have shown that the greatest benefit in

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pregnancy to the mother and fetus is improved glycemic control. Therefore, the risk of disruption in glycemic control should be weighed when considering a product change. There are no data to date regarding use of the rapid-acting insulin analogs in lactation, and the extent of secretion of these agents in breast milk is not known. The decision to breast-feed and the choice of insulin products should be evaluated on an individual basis. As with other insulins, rapid-acting insulin analogs should be monitored carefully, as pregnant and lactating women are in a continual state of physiologic change and experience frequent changes in insulin requirements.

Rapid-acting insulin analogs have also been found to be safe and

effective in children with Type 1 diabetes. Due to children's unpredictable behavior and eating patterns, rapid-acting insulin analogs may offer a benefit over RHI in the flexibility of administration at the time of the meal.

Differences among rapid-acting insulin analogs

As discussed above, the rapid-acting analogs are very similar in pharmacokinetics, safety, and efficacy. Clinical studies comparing the agents in weight gain or effects other than glycemic control may set them apart in the future. Currently, the determining factor usually lies with health insurance and prescription coverage.

Table 4
Insulin analog delivery device availability

Delivery device	Aspart	Lispro	Glulisine	Glargine	Detemir
Vial	10 ml 100 units/ml	10 ml 100 units/ml	10 ml 100 units/ml	10 ml 100 units/ml	10 ml 100 units/ml
Prefilled pen	3 ml 100 units/ml	3 ml 100 units/ml	n/a	n/a	3 ml 100 units/ml
Compatible disposable pen	NovoLog FlexPen	HumaLog Pen	n/a	n/a	Levemir FlexPen
Cartridges	3 ml 100 units/ml	3 ml 100 units/ml	3 ml 100 units/ml	3 ml 100 units/ml	3 ml 100 units/ml
Pens that fit cartridges	NovoPen 3, NovoPen Jr, Innovo, InDuo	Autopen	OptiClik	OptiClik	NovoPen 3, NovoPen Jr, Innovo, InDuo
CSII	Yes	Yes	Yes	No	No

CSII = Continuous subcutaneous insulin infusion

n/a = not available

LONG-ACTING INSULIN ANALOGS

As with bolus insulin therapy, the long-acting insulin analogs are providing options that more closely mimic our body's natural basal insulin effects (see Table 3). Two agents that are now currently available, insulin detemir and insulin glargine, offer a duration of action up to 24 hours, minimal peaking effect, and less interpatient variability in dosing. These agents are also devised through recombinant DNA technology.

Safety and efficacy

Clinical studies comparing insulin detemir and insulin glargine in patients with Type 1 and Type 2 diabetes found similar reductions in HbA_{1c}. However, the long-acting insulin analogs provided lower fasting blood glucose readings and less nocturnal hypoglycemia compared with NPH insulin. A comparison of insulin detemir and NPH once daily at bedtime with mealtime RHI found comparable HbA_{1c} levels; however, insulin detemir had significantly greater reductions in fasting blood glucose and risk of hypoglycemia. Patients

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receiving insulin detemir also experienced significantly less weight gain compared with those using NPH.

The impact of the reduction in nocturnal hypoglycemia was also found with insulin glargine compared with NPH in addition to current oral antihyperglycemic agents in patients with Type 2 diabetes. The HbA_{1C} was reduced similarly in each group, with the insulin glargine group having significantly less nocturnal hypoglycemia and lower post-dinner glucose concentrations. Weight gain was comparable among groups.

Insulin detemir twice daily and insulin glargine once daily were compared in patients with Type 1 diabetes utilizing mealtime insulin aspart. Although similar reductions in HbA_{1C} were seen between groups, treatment with insulin glargine resulted in significantly lower fasting plasma glucose levels. Overall, hypoglycemic episodes were similar between groups; however, patients receiving insulin detemir experienced significantly fewer major hypoglycemic episodes and nocturnal hypoglycemia compared with the insulin glargine group. Weight gain between the two groups was not statistically significant. Once-daily detemir administration has not yet been compared with once-daily glargine.

Dosing

Dosing of insulin detemir and insulin glargine differ slightly. Insulin detemir may be administered once or twice daily. Patients with Type 1 or Type 2 diabetes treated with basal/bolus therapy may be transitioned to insulin detemir on a unit-to-unit basis of the basal insulin. For insulin-naïve patients with Type 2 diabetes who are on oral antihyperglycemic agents, insulin detemir may be initiated at 0.1 to 0.2 units/kg once daily or 10 units once or twice daily.

Insulin glargine should be administered every 24 hours. When changing therapy in patients already receiving a once-daily dose of basal insulin to insulin glargine, a 1:1 conversion is recommended.

However, for patients receiving basal dosing two or more times per day, a 20% reduction in the total daily basal dose is recommended for conversion to the insulin glargine dose. For insulin-naïve patients with Type 2 diabetes on oral antihyperglycemic agents, insulin glargine may be initiated at 10 units at bedtime.

Conversion between insulin detemir and glargine may occur on a 1:1 basis. For both insulin detemir and glargine, daily monitoring of fasting blood glucose and dose adjustments may be made on a weekly basis to adjust insulin doses to meet glycemic goals.

Administration

Long-acting insulin analogs are clear solutions; therefore, no mixing is required prior to injection. They are available in vials, disposable pen devices, and cartridges for reusable pen devices. Timing of the doses is patient-dependent as long as the doses occur at the same time each day. Insulin detemir and glargine may be given once a day at bedtime or before breakfast. For twice-daily dosing of detemir, similar outcomes were found with dosing every 12 hours versus before breakfast and dinner.

Long-acting insulin analogs are not to be given by intravenous infusion or by continuous subcutaneous insulin infusion (CSII) due to their long duration of action. Long-acting insulin analogs should not be mixed with any other insulin products, including rapid-acting analogs, as the pharmacokinetic properties of the insulins are altered. If insulin detemir or glargine is given at the same time as RHI or a rapid-acting analog, a separate syringe and injection site within the same area should be utilized. The stability of the long-acting insulin analogs varies. An opened vial of insulin glargine is stable for 28 days, while insulin detemir is stable for 42 days.

Adverse reactions

Although the risk of hypoglycemia is less than with NPH, it remains

Table 5
Insulin pen devices

Pen name	Manufacturer	Features
FlexPen	Novo Nordisk	Disposable, prefilled Large dose-dialing windows Easy dose correction 3 ml of aspart or detemir insulin
		1-unit increment dosing Dosing range 1-60 units Airshot/priming required with 2 units before each injection
NovoPen3	Novo Nordisk	Reusable metal construct Easy dose correction 3-ml aspart and detemir cartridges
		1-unit increment dosing Dosing range 2-70 units Airshot/priming required with 2 units before each injection
Innovo	Novo Nordisk	Reusable pen device Built-in memory Compact and easy to transport Easy dose correction
		1-unit increment dosing Dosing range 2-70 units Large digital display for easy viewing 3-ml aspart and detemir cartridges are compatible Airshot/priming required before each injection
Humalog Pen	Eli Lilly	Disposable, prefilled pen Easy dose correction Prefilled with insulin lispro
		1-unit dosing increments Dosing range 1-60 units Airshot/priming required before each injection
Autopen	Owen Mumford	Reusable pen device Large-size unit numbers Audible clicks upon dialing Compatible with lispro cartridges
		2 models: fits either 1.5-ml or 3-ml lispro cartridges Model one has 1-unit dosing increments from 1-21 units Model two has 2-unit dosing increments up to 42 units Mounted activation button for automatic insulin delivery Airshot/priming required with 2 units before each injection
OptiClik	Sanofi-Aventis	Reusable pen device Large-size unit numbers Audible clicks
		1-unit dosing increments Dosing range from 1-80 units Compatible with 3 ml glargine and glulisine insulins Airshot/priming required with 1 unit before each injection
Innolet	Novo Nordisk	Disposable, prefilled pen Largest available dial Most legible numbers Audible clicks Large grip Compact and easy to transport
		1-unit dosing increments Dosing range from 1-50 units Prefilled with Novolin N, Novolin R, Novolin 70/30 Not compatible with insulin analogs Designed for patients with poor eyesight and dexterity Easy dose correction Airshot/priming required with 2 units before each injection

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the most common and severe reaction of long-acting insulin analogs. Hypoglycemia most likely occurs in patients who have alterations in meal habits, illness, increase in physical activity, or are near normoglycemia. Patients should be counseled on the signs and symptoms of hypoglycemia and instructed when to seek medical attention.

Allergic reactions, such as pruritus and rash, and injection-site reactions, such as lipodystrophy, are similar to reactions found with NPH insulin. Patients should be counseled to immediately report any signs of a systemic or localized reaction to their physician.

Use in special populations

As with the other insulin preparations, a decrease in renal clearance occurs with declining renal function, resulting in increased insulin effects. An increase in circulating insulin levels was also detected in patients with hepatic impairment. Therefore, cautious dose adjustments and increased blood glucose monitoring are recommended in these patients.

As with the rapid-acting insulin analogs, there are sparse clinical data on the use of long-acting insulin analogs in pregnancy and lactation, and these agents are not recommended to be used for gestational diabetes at this time. The use of insulin and the risks and benefits should be discussed with any woman with diabetes planning to become pregnant.

Insulin detemir and insulin glargine have been found safe and effective in children over six years of age.

DELIVERY DEVICES FOR INSULIN ANALOGS

The insulin analogs are available as the conventional vial and syringe

delivery system as well as newer devices (see Table 4). Insulin aspart, lispro, and detemir are available as vials, prefilled disposable pens, and cartridges, which are to be used in a reusable pen. Insulin glulisine and glargine are available as a vial and as cartridges to be used in reusable pens. The rapid-acting analogs may also be used for CSII.

Selecting an injectable insulin delivery device

When aiding a patient in choosing which insulin delivery device best suits his or her needs, the clinician must consider patient preference, medical efficacy of the delivery system, the presence of any physical limitations that would impede correct dosing and administration, and the availability of a patient's insulin formulation in a particular delivery system. These factors greatly affect compliance with an insulin therapy regimen and must be evaluated before an insulin device is chosen in order to optimize the success of patient-specific insulin therapy.

The insulin analog formulations are all available as 3-ml cartridges to be used in reusable pens, and most of the formulations are also available as prefilled disposable pens. A review of the features of each insulin delivery device is provided in Table 5.

Conclusion

In conclusion, the new insulin analogs and their available delivery systems offer patients and providers more options to achieve their glycemic goals. Pharmacists can assist their patients and providers by evaluating the available options and providing them with the necessary information to make the most informed choices in the medical care of their diabetes condition.

References are available upon request.

TEST QUESTIONS

Mark the most appropriate answer. The answer form follows the test questions.

- Which of the following statements is *true* regarding normal physiologic bolus insulin secretion?
 - It occurs in response to a meal stimulus.
 - Peak effect usually occurs in one hour.
 - It has a relatively short duration of action.
 - All of the above are true.
- Which of the following statements is *false* regarding healthy basal insulin secretion?
 - It is constantly released over a 24-hour period.
 - It accounts for 100% of the body's actual insulin secretion.
 - There is no pronounced peak effect.
 - It suppresses glucose production between meals and overnight.
- Which of the following are limitations when using NPH insulin as a basal insulin?
 - The duration of action is less than 24 hours
 - Patients require multiple injections
 - NPH demonstrates a peak effect roughly six to eight hours after injection
 - All of the above
- Which of the following is *not* a rapid-acting insulin analog?
 - Insulin aspart
 - Insulin glulisine
 - Insulin glargine
 - Insulin lispro
- Which of the following is an advantage of using a rapid-acting insulin analog compared with regular human insulin (RHI) for bolus insulin therapy?
 - Increased flexibility in meal timing
 - Less nocturnal hypoglycemia
 - Improved lowering of postprandial blood glucose
 - All the above
- Which of the following is the appropriate dose to switch a patient taking 12 units of RHI before breakfast and dinner to insulin lispro?
 - 5 units before breakfast and dinner
 - 9 units before breakfast and dinner
 - 12 units before breakfast and dinner
 - 15 units before breakfast and dinner
- Which of the following administration instructions is correct?
 - Insulin aspart should be injected within five to 10 minutes of starting a meal.
 - Insulin glulisine should be injected 30 minutes before or 30 minutes after the start of a meal.
 - Insulin lispro should be injected within five minutes of the start of a meal or up to 20 minutes after.
 - All the above are correct.
- Which of the following is a determining factor in deciding which rapid insulin analog to choose?
 - Prescription formulary coverage
 - Choice of basal insulin
 - Desired number of daily injections
 - Side-effect profile
- Which of the following is an advantage of using a long-acting analog compared with NPH insulin?
 - Less risk of nocturnal hypoglycemia
 - Greater reduction in fasting plasma glucose
 - Less interpatient variability in dose titration
 - All the above

TEST QUESTIONS

- 10.** A patient receiving 30 units of NPH twice daily would appropriately be switched to which of the following doses of insulin glargine?
- a. 30 units once daily
 - b. 30 units twice daily
 - c. 48 units once daily
 - d. 24 units twice daily
- 11.** For a patient not receiving basal insulin therapy, what is an appropriate dose for initiating insulin detemir?
- a. 10 units once daily
 - b. 10 units twice daily
 - c. 0.1-0.2 units/kg once daily
 - d. All the above
- 12.** Which of the following insulin combinations is stable if mixed in the same syringe for injection?
- a. Insulin glargine and insulin glulisine
 - b. Insulin detemir and insulin aspart
 - c. NPH insulin and insulin lispro
 - d. RHI and insulin detemir
- 13.** Which of the following statements is *false* regarding the use of the long-acting insulin analogs?
- a. These agents should be administered at the same time each day.
 - b. There are limited clinical studies demonstrating safe use of these agents during pregnancy.
 - c. Conversion between insulin detemir and insulin glargine may occur on a 1:1 basis of the total daily dose.
 - d. These agents may be given by intravenous infusion.
- 14.** Which of the following statements is *true* regarding the storage of insulin analogs?
- a. An opened vial of insulin detemir is stable at room temperature for up to 42 days.
 - b. Each rapid-acting insulin analog is available in premixed solutions.
 - c. Premixed disposable pens containing rapid-acting insulin analogs are stable at room temperature for up to 28 days.
 - d. An open vial of insulin glargine may be used until empty as long as it is stored in the refrigerator between uses, even if longer than 28 days.
- 15.** Which of the following counseling points is important to consider with patients taking an insulin analog?
- a. Alterations in timing of insulin injections
 - b. Alterations in insulin dose to be administered
 - c. Potential confusion of insulin vial or pen products by similar appearance
 - d. All the above
- 16.** Which of the following is *not* a reusable pen device?
- a. OptiClik
 - b. Innovo
 - c. NovoPen3
 - d. FlexPen
- 17.** Which of the following should *not* be used for continuous subcutaneous insulin infusion?
- a. Insulin aspart
 - b. Insulin glargine
 - c. Insulin glulisine
 - d. Insulin lispro
- 18.** Which of the following insulin delivery devices is *not* available for insulin analogs?
- a. OptiClik
 - b. Innolet
 - c. Autopen
 - d. Innovo
- 19.** Which of the following statements is *false* regarding the FlexPen insulin delivery device?
- a. It is available for insulin aspart and insulin detemir.
 - b. Its dose changes are available at a minimum of 1 unit.
 - c. It has easy dose correction.
 - d. It has a dosing range from 1 to 80 units.
- 20.** Insulin aspart is available as:
- a. A vial, a prefilled pen, and an insertable cartridge
 - b. A vial and a prefilled pen
 - c. A vial and a 3-ml insertable cartridge
 - d. A vial only

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ANSWER FORM

**Advances in diabetes therapy:
Rapid- and long-acting insulin analogs**

OCTOBER 9, 2006 ACPE # 012-999-06-164-H01

Test questions start on page 66

- | | | | |
|----------------|----------------|-----------------|-----------------|
| 1. a. b. c. d. | 5. a. b. c. d. | 9. a. b. c. d. | 13. a. b. c. d. |
| 2. a. b. c. d. | 6. a. b. c. d. | 10. a. b. c. d. | 14. a. b. c. d. |
| 3. a. b. c. d. | 7. a. b. c. d. | 11. a. b. c. d. | 15. a. b. c. d. |
| 4. a. b. c. d. | 8. a. b. c. d. | 12. a. b. c. d. | 16. a. b. c. d. |

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