Diabetes Treatment: Insulin and Incretins

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Editor's note: *This article is the fourth in an eight-part series reviewing the fundamentals of diabetes care for physicians in training. This series is an updated adaptation of a 12-part series published in* Clinical Diabetes *between 2006 and 2009. The previous series, and earlier installments of this one, can be found online at the journal Web site (http://clinical.diabetesjournals.org).*

Part 1: Insulin Basics

Insulin is the original and the most effective treatment to control glucose levels in diabetic patients. It was first used in the treatment of diabetes by Frederick Banting and Charles Best in 1922. Although originally thought to be a cure for diabetes, it soon became evident that insulin was a method of controlling the disorder. We now know that insulin may be used to control the hyperglycemia of virtually any form of diabetes. Although it was initially prepared by isolation from animal pancreatic tissue, insulin is now prepared through recombinant DNA techniques using microorganisms. Use of recombinant insulin has decreased the immunogenicity of commercially available insulin.

Type 1 diabetes is characterized by a loss of pancreatic β-cells and therefore an absolute insulin deficiency. The mainstay of therapy, therefore, is insulin treatment. Because the disease does not affect insulin sensitivity, patients typically require small doses of insulin to maintain glucose control. By contrast, type 2 diabetes is characterized by preexisting insulin resistance followed by a relative insulin deficiency. As a result of insulin resistance and progressive insulin deficiency, patients with type 2 diabetes typically require higher doses of insulin with gradual upward titration of doses.

Since the discovery of insulin and its use to treat diabetes, insulin has been combined with additives and even modified at the molecular level to change its pharmacokinetic properties. Some insulin preparations accelerate insulin's effects in the bloodstream, whereas others prolong the pharmacokinetic profile. These insulin preparations may be used alone or in combination with other insulins in formulating an insulin regimen.

Short- and rapid-acting insulins

Regular insulin was the first available insulin preparation and therefore the first short-acting insulin. At the time of injection, regular insulin self-associates to form hexamers, which are poorly absorbed into the circulation. Gradually, insulin hexamers dissociate into dimers and monomers, which enter the bloodstream more rapidly. Formation of hexamers therefore delays absorption and activity of regular insulin.

Regular insulin tends to have an onset of action 30–60 minutes after injection, a peak effect in 2–3 hours, and a total duration of action of 8–10 hours. Because of the delayed onset of regular insulin, patients are typically instructed to inject it ~ 30 minutes before meals. This can be more cumbersome than the use of insulin analogs, which can be injected much closer to mealtimes.

Another disadvantage of regular insulin is that its pharmacokinetic profile does not overlap with the rate of carbohydrate absorption as well as that of insulin analogs. As a result, regular insulin can produce more postprandial hyperglycemia soon after meals and delayed hypoglycemia several hours after meals. This effect may be more pronounced in patients with type 1 diabetes because of their relatively high insulin sensitivity.

Regular insulin have some advantages over other insulin formulations, however. Because it is bioidentical to endogenous insulin, immunogenicity is very low—much lower than with animal insulin preparations. Cost is also a major advantage; regular human insulin sells for about one-fourth the price of insulin analogs.[1–3]

There are currently three rapid-acting insulin analogs available in the United States: lispro, aspart, and glulisine. All three feature modifications to the insulin molecule that cause rapid dissociation of hexamers into dimers and monomers after injection.

Rapid dissociation leads to rapid absorption. As a result, these formulations may be administered at the beginning of a meal, which

many patients find more acceptable and easier to remember than having to inject a full 30 minutes before meals.[4]

All rapid-acting insulin preparations are available in both vial and pen devices. Insulin lispro and insulin aspart each have an onset of action of 5–15 minutes, a peak of activity in 30–90 minutes, and duration of action of 4–6 hours. These insulins deliver approximately twice the maximal concentration of insulin and take approximately half as much time to reach maximal concentrations as regular insulin injected subcutaneously.[4,5] Glulisine, the newest of these agents, has a faster onset than lispro.[6] As a result, it may be administered after meals rather than immediately before them.

Rapid-acting insulins exhibit better control of postprandial glucose levels and have a lower frequency of causing postprandial hypoglycemia than regular insulin. There may also be less variability in insulin levels from injection to injection with rapid-acting insulin analogs.[1] A major disadvantage of rapid-acting analogs, however, is price. The cost of these products is approximately four times that of regular human insulin.

Intermediate- and long-acting insulins

The effects of regular insulin may be delayed and prolonged by several modifications to either the solution containing the insulin or to the insulin molecule itself. The result of such changes is a pharmacokinetic profile that allows the product to be used to replace the body's basal insulin requirements.

Currently, there are one intermediate- and two long-acting insulins available in the United States. The addition of protamine to regular insulin yields neutral protamine Hagedorn (NPH) insulin. The onset of action of NPH insulin is typically 2–4 hours, with a peak in activity within 4–10 hours and an effective duration of 10–16 hours. Because of its peaking action, NPH is associated with a higher incidence of hypoglycemia than are the analogs detemir and glargine, which tend to have less peaking action. NPH may be used two or three times daily as a basal insulin or used in the morning to act as a combination of basal and bolus insulin to cover the noon meal.

Two rapid-acting insulins, lispro and aspart, are also available in protamine solutions that prolong their effects. When in such solutions, their long-acting component is similar to NPH.[5]

NPH insulin is inexpensive and available without a prescription. However, it has other potential disadvantages, such as significant intra-patient variation in absorption, which may cause variations in peak and duration from one injection to another.[3,7]

The action of insulin may also be prolonged by adding zinc. Such a solution yields lente and ultralente insulin, which are no longer available in the United States.

Long-acting insulin attempts to replicate the body's basal insulin secretion. Currently, glargine and detemir insulins are available for such therapy. Both are available in vial and pen forms.

Glargine was originally released in 2001. Like short-acting insulin analogs, glargine is a modified insulin molecule that contains changes in amino acids to alter the absorption of glargine into the bloodstream. These substitutions in glargine, however, affect its solubility such that it is only soluble in an acidic solution (which is present in the vial of insulin). Once injected beneath the skin, the buffering action of interstitial fluid neutralizes the pH such that glargine is no longer soluble and precipitates under the skin to form a reservoir of insulin. It is the precipitation of insulin out of solution that produces the extended half-life of glargine, which approaches 24 hours.[3,4] The prolonged action of the insulin reduces the peaking effect and results in a lower risk of hypoglycemia than NPH.

Glargine is administered once daily, which may improve compliance. However, it is two to three times more expensive than NPH and has not been shown conclusively to reduce A1C compared to NPH. Injection of glargine, especially in larger doses, may cause a burning sensation, likely as a result of the acidity of the solution.

Detemir was introduced more recently and uses a different approach to extend its half-life. The insulin molecule is bound to a 14-carbon fatty acid. The addition of the hydrophobic fatty acid leads to albumin affinity, allowing the insulin to travel through the bloodstream bound to albumin.

Because only the free fraction of the insulin molecule is active, the effective half-life of detemir is prolonged compared to regular insulin. Its duration is 14–21 hours at commonly prescribed doses, but like other insulin formulations, the duration is longer at higher doses. Detemir may also have a more predictable glucose-lowering effect than NPH insulin.[8,9] It is approved for use once or twice daily.

Detemir is associated with a lower risk of hypoglycemia than NPH in patients with type 1 or type 2 diabetes.[9,10] Like glargine, it is available in pen or vial, but also like glargine, it has the disadvantage of being much more expensive than NPH. Also, it has not been shown definitively to improve A1C compared to NPH.

Insulin regimens

Traditionally, glucose has been controlled using an injection of NPH and regular insulin in the morning and in the evening. Because these insulins may be mixed, this approach minimizes the number of injections required.

Regular insulin from the morning injection acts to control glucose levels after breakfast, with the extended action of regular insulin acting to assist in basal insulin requirements. NPH insulin, because of its combination of prolonged effect and peak in 4–10 hours, both serves as basal insulin and controls glucose after the midday meal. The second injection of regular and NPH insulin is typically given at suppertime. As in the morning, the regular insulin component provides for glucose control after the evening meal, and the NPH component provides for basal insulin needs overnight. Additional regular insulin may be used at breakfast and supper for correction of hyperglycemia.

This traditional approach can be problematic, however. The overlap of regular insulin with NPH activity can cause considerable drops in glucose level, which often requires midmorning and bedtime snacking to avoid hypoglycemia. Patients must also maintain a relatively inflexible daily schedule in which they eat lunch on time and consume predetermined amounts of carbohydrate based on the amount of NPH they have injected hours ahead of time. Delaying lunch would typically result in hypoglycemia, whereas delaying breakfast or supper could cause hyperglycemia as the effects of NPH wane.[4]

A newer approach to administering insulin involves using the new long-acting analogs (glargine or detemir) to provide basal insulin coverage with one or two injections daily and rapid-acting insulin analogs (lispro, aspart, or glulisine) to cover mealtime glucose excursions. This more intensive approach requires at least four injections daily and attempts to more closely replicate the body's physiological insulin secretion. As a result, patients have greater flexibility regarding the timing of their meals and typically do not have to eat at a particular time of the day to avoid hypoglycemia (as long as their dose of basal insulin is not too high). Rapid-acting insulin is usually dosed according to the amount of carbohydrate consumed at each meal. Patients should check glucose levels at each meal and administer additional rapid-acting insulin if necessary.[4]

Using a true basal insulin rather than NPH is associated with a lower risk of hypoglycemia in patients with type 1 or type 2 diabetes.[5,7,11,12] However, this approach has not clearly resulted in improved A1C levels in large studies. It should also be noted that the expense of using two different insulin analogs is much greater than that of using regular and NPH insulins.

Initiation of insulin therapy

A common dilemma that faces many physicians is the initiation of insulin in patients with type 2 diabetes. Because type 1 diabetes is caused by absolute insulin deficiency, all patients will require insulin administration. Insulin therapy should therefore be initiated at the time of diagnosis with type 1 diabetes, and intensive insulin therapy as described above is the preferred approach. Type 2 diabetes is characterized by a slower decline in pancreatic β-cell function and the eventual need for insulin therapy, but the timing of insulin initiation can be a topic of debate among physicians and a source of dread on the part of patients.

According to a recent joint consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes, indications for insulin therapy in type 2 diabetes include an A1C level > 7% despite lifestyle modification and the use of metformin. Insulin may be delayed until after addition of a sulfonylurea, a thiazolidinedione, or both has failed to adequately control glucose levels.

Insulin is typically initiated in the form of basal insulin added to existing oral agents at a dose of 0.2 units/kg body wt/day and increased every 5 days until the fasting glucose level is < 100 mg/dl.[3,13] However, some studies have suggested that initiation of a premixed insulin formulation (insulin that contains a short- or rapid-acting component and a long-acting component) may be an acceptable alternative.[14] As insulin deficiency progresses in type 2 diabetes, mealtime insulin may be added to control postprandial glucose levels and to allow for correction of hyperglycemia.

Important considerations

When initiating and adjusting insulin therapy, it is important to remember that certain situations mandate greater caution regarding the potential for hypoglycemia. ADA recommends that all patients using multiple insulin injections should check their blood glucose level three or more times daily and that, even in patients using less frequent insulin injections, self-monitoring of blood glucose is useful.[15] This is especially useful for avoiding hypoglycemia. It is important to counsel patients about the importance of not driving, swimming, or operating heavy machinery when they are hypoglycemic; glucose levels should be assessed before they perform such activities.

Certain patient populations have a higher risk of developing hypoglycemia. Patients with renal or hepatic dysfunction may have

a higher likelihood of developing hypoglycemia. The liver and kidneys are responsible for virtually all of the body's gluconeogenesis and glycogenolysis, as well as for degradation of insulin. Patients with hepatic or renal insufficiency therefore have a combination of less endogenous glucose production and a longer insulin half-life, which can expose them to rapid glucose drops. It is important to initiate insulin at lower doses in these patients and to instruct them to remain vigilant for hypoglycemia.

Other patients who may experience a higher risk of hypoglycemia are those with pancreoprivic diabetes mellitus (injury or removal of the pancreas). These patients, in addition to losing β-cells, also have a deficit of pancreatic α-cells. The result is glucagon deficiency and impaired recovery from hypoglycemia. It is important to instruct these patients about the signs, symptoms, risks, and treatment of hypoglycemia. They may also require a prescription for an emergency glucagon kit, although it is possible that patients with hepatic insufficiency may have an impaired response to glucagon. Patients should also be instructed to wear medical alert identification.

Part 2: Incretins

Incretins are gastrointestinal peptides that affect glycemic control. Their existence was hypothesized when it was noted that oral glucose stimulated two to three times more insulin release than the same amount of glucose administered intravenously. Subsequent investigation revealed the presence of several hormones that play a significant role in postprandial glucose control, including amylin, gastric inhibitory peptide (GIP), and glucagon-like peptide 1 (GLP-1).

During the past few years, analogs of these hormones have become available for use in controlling diabetes. Because they have only recently been commercially available for the treatment of diabetes, many of the mechanisms of action and long-term effects are not fully understood.

Pramlintide therapy

Pramlintide is an analog of amylin, a naturally occurring hormone produced by pancreatic β-cells. Amylin levels increase postprandially and typically correlate with insulin levels. As with insulin, amylin levels are very low in type 1 diabetes. However, levels may be elevated in patients with insulin resistance.[16,17]

Administration of exogenous amylin in the form of pramlintide has been shown to decrease postprandial hyperglycemia in insulin-treated patients with type 1 or type 2 diabetes. The major mechanism of action appears to be inhibition of gastric emptying and suppression of glucagon release. Clinically, it also suppresses appetite in patients who receive it.

The improvement in overall glucose control has been modest in clinical trials, at around 0.3%. However, those using the medication have also experienced weight reduction of ~ 1–1.5 kg in patients with type 1 diabetes and ~ 2.0–2.5 kg in patients with type 2 diabetes.

The usual starting dosage for patients with type 1 diabetes is 15 µg before meals, titrated eventually to 60 µg.Patients with type 2 diabetes usually start with a dose of 60 µg at mealtimes, which is eventually titrated to 120 µg.

Use of pramlintide has been shown to increase the risk of insulin-induced severe hypoglycemia in patients with type 1 diabetes. Therefore, patients should start at a low dose as described above and should also decrease their prandial insulin doses by 50% and closely monitor themselves for hypoglycemia.[18–22] It should also be noted that pramlintide therapy is relatively expensive compared to generic insulin but is available in a pen for easy administration. It is indicated for insulin-treated patients with type 1 or type 2 diabetes.

Exenatide and liraglutide

Exenatide and liraglutide are analogs of GLP-1, a naturally occurring incretin produced by the L-cells of the distal ileum. GLP-1 stimulates insulin release from the pancreatic β-cells, suppresses glucagon release from the pancreatic α-cells, slows gastric emptying, and acts on the brain to increase satiety.[17,23,24] Response to GLP-1 may be slightly blunted in type 2 diabetes.[25] Interestingly, increases in GLP-1 may be responsible for some of the weight loss following roux-en-Y gastric bypass surgery in patients with type 2 diabetes.[26]

Administration of exenatide in patients with type 2 diabetes has similar effects. Clinically, the result is an A1C reduction of ~ 1%. Preliminary studies suggest that a significant proportion of insulin-treated patients with type 2 diabetes may be successfully transitioned from insulin to exenatide in addition to their oral agents.[27] Most patients experience significant weight loss of ~ 2.5 kg when exenatide is used in addition to metformin and ~ 1 kg when it is added to a sulfonylurea.[17,28–30]

Liraglutide works in a similar manner to exenatide but has a longer half-life, which allows for once-daily (rather than twice-daily) dosing. Some studies, including one meta-analysis, suggest that it may have a slightly greater A1C-lowering effect than exenatide, although more investigation is warranted to substantiate such findings.[31,32] Neither exenatide nor liraglutide are indicated for simple weight loss.

Patients using exenatide typically take 5 µg before breakfast and supper, and the dose is increased to 10 µg before breakfast and supper after about 1 month. To ease administration, exenatide is available in 5- or 10-µg pens with premeasured dosing.

Likewise, liraglutide dosing is typically started at low doses and increased as tolerated. Typically, patients begin taking 0.6 mg subcutaneously once daily, and the dose is titrated weekly as tolerated to 1.8 mg once daily.

Like pramlintide, the costs of liraglutide and exenatide are relatively high compared to that of generic insulin and other generic medications. Neither exenatide nor liraglutide are approved for use in the treatment of type 1 diabetes. Both are indicated for use with sulfonylureas, metformin, or thiazolidinediones. Exenatide is approved for monotherapy, but liraglutide is not recommended for use as monotherapy. Rodent studies have shown propensity for c-cell hyperplasia and tumor growth in response to high GLP-1 levels, although there is not evidence of tumor growth in humans.[33]

Conclusions

Although injected medications such as GLP-1 agonists, insulin, and insulin analogs are viewed with trepidation among many patients, their effectiveness merits their use in clinical medicine. The margin of safety can be narrow with such medications, especially insulin and insulin analogs. With the aging of the U.S. population and the rapid increases in rates of obesity, the prevalence and severity of diabetes will undoubtedly increase considerably for the foreseeable future. It is important for medical professionals to understand, initiate, and adjust treatment with the above medications to provide for the appropriate care, safety, and well-being of patients with diabetes.

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