Is There a Need for a Better Basal Insulin?

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Diabetes is one of the most common noncommunicable diseases.[1] It is a leading cause of death in developed countries and is epidemic in newly industrialized countries.

Complications associated with uncontrolled diabetes include blindness, renal failure, neuropathy, peripheral vascular disease, infection, and amputation. These outcomes are not inevitable; they can be prevented or delayed through strict metabolic control of blood glucose.[2,3] Attempts to achieve and maintain good glycemic control are aided by a growing armamentarium of insulin formulations.

The routine use of intensive insulin therapy by people with type 1 diabetes and increasing use of insulin by people with type 2 diabetes[4] has fueled efforts to produce better insulin formulations. To date, most research has been directed toward optimization of short-acting insulins, whereas new developments in long-acting insulins have lagged. Indeed, there have been no innovations in long- and intermediate-acting insulins in nearly 50 years,[5] despite multiple attempts to produce insulins without the pharmacokinetic shortcomings of existing formulations.

Thanks to advances in recombinant DNA technology, however, researchers are attempting to design long-acting insulin analogs that lack the variable absorption and pharmacological limitations of currently available depot insulin preparations.[6] Results of preclinical and clinical studies of these newer insulins have demonstrated varying degrees of success. Results of clinical trials of insulin glargine, a recently approved long-acting insulin analog, and a variety of basal insulins now in clinical development suggest that these newer agents may provide benefits compared with the older long-acting insulin formulations.

The Role of Basal Insulin

The goal of diabetes treatment is to mimic the physiological secretion of insulin in healthy people. Insulin is secreted in response to carbohydrate ingestion into the portal circulation from pancreatic β-cells in two phases: a rapid initial release followed by a slower, longer-acting phase that begins about 10 min after eating and lasts ~60 min.[7] Additionally, a basal amount of insulin is secreted continuously at a rate of about 0.5 U/h to meet between-meal and overnight glucose-regulating requirements and to suppress excess hepatic glucose production.[8]

Typically, people with type 1 diabetes attempt to model physiological insulin secretion by using a basal-bolus insulin regimen that combines a once- or twice-daily injection of an intermediate- or long-acting insulin to meet basal insulin requirements with bolus injections of a short-acting insulin before meals to meet prandial needs.

IN BRIEF

Basal insulin therapy is an integral part of intensive management of type 1 diabetes and is often used in conjunction with oral agent therapy for type 2 diabetes. Currently available insulins do not always provide adequate background coverage. Insulin glargine, a new product that will soon be available for commercial use, addresses this need by providing 24-h coverage without peaks or valleys.

The short-acting, monomeric insulin lispro is effective for preventing postprandial glucose excursions and can be more convenient to use than regular insulin. However, clinical study results have not consistently shown insulin lispro to improve overall glycemic control as illustrated by HbA_{1c} concentrations.[9] This is thought to be because of the observed late postprandial blood glucose rise as the effect of insulin lispro wanes in the presence of inadequate substitution of basal insulin.[9] For example, in a 3-month study of type 1 diabetic patients in which lispro was used with once-daily NPH insulin, HbA_{1c} was not improved and fasting blood glucose was significantly increased.[10] In contrast, a study of insulin lispro used in combination with continuous subcutaneous insulin infusion (CSII) of regular insulin demonstrated statistically significant reductions in HbA_{1c}.[11] Thus, an effective long-term intensive regimen with insulin lispro in people with type 1 diabetes must include adequate basal insulin replacement.[12,13]

The glycemic abnormality in type 2 diabetes appears to be a combination of insulin deficiency caused by β-cell dysfunction and insulin resistance.[14] Therefore, people with type 2 diabetes typically begin pharmacological treatment with oral insulin secretagogues and/or insulin sensitizers.

Type 2 diabetes is a progressive disease, and antidiabetic agents such as sulfonylureas and metformin are associated with a high rate of secondary failure.[15] Although physicians are often reticent to prescribe insulin therapy for these patients, a long-acting basal insulin can effectively treat both insulin deficiency and insulin resistance.[13]

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Basal-bolus insulin regimens are infrequently used in managing type 2 diabetes. Instead, therapy may consist of a once-daily long-acting subcutaneous insulin in combination with oral agents.[4] There is concern about undue weight gain. However, at appropriate doses, a basal insulin need not induce marked weight gain.[14]

The first successful longer-acting exogenous insulins, protimine zinc, globin, and neutral protamine Hagedorn (NPH) and the lente insulins, were produced in the 1930s[16] and 1950s,[17] respectively, and continue to be widely used to meet basal insulin requirements. Unfortunately, the pharmacokinetic and pharmacodynamic effects of these insulins often contribute to significant hypo- and hyperglycemia.[12]

Limitations of Available Basal Insulins

NPH insulin. NPH human insulin is a crystalline suspension formed by adding a basic protein (protamine) to insulin, rendering it less soluble at neutral pH and extending its duration of action. A single dose of NPH is inadequate for use with the short-acting insulin lispro.[5]

The number of injections of NPH per day is not of great concern. However, the action profile of NPH can make evening administration problematic. NPH has an onset of action within 2 h of injection, peaks approximately 6 h after injection, and has a duration of effect ranging from 13 to 20 h (Table 1). Thus, a pre-supper injection is not sustained overnight, and fasting hyperglycemia results.[18]

Administering NPH at bedtime can also be risky. An injection at 10:00 p.m. provides maximum hypoglycemic action between 3:00 and 5:00 a.m., when insulin requirements are relatively low. This increases the risk of nocturnal hypoglycemia. Attempts to prevent hypoglycemia by decreasing the nighttime dose can lead to relative insulin deficiency between 5:00 and 8:00 a.m., a time when insulin sensitivity is decreased. Morning fasting hyperglycemia is a well-known shortcoming of NPH therapy.[5]

Lente insulins. The intermediate-acting human lente insulins are crystalline suspensions of insulin with zinc ions added to prolong duration of action. Human lente insulins have a slightly longer pharmacokinetic profile than NPH (Table 1), although variations in absorption with both insulins can make it difficult to distinguish between their time-action profiles.[18] Human ultralente insulin is the longest-acting human insulin. It exhibits peak activity between 8 and 14 h after injection, with glucodynamic effects lasting up to 30 h.[9]

The use of ultralente as a basal insulin is controversial. Several studies suggest that ultralente does not provide true basal insulin coverage. Instead, its pharmacokinetics are similar to those of NPH and lente insulins. Moreover, ultralente insulin is associated with high levels of severe hypoglycemia.[18]

The most significant shortcoming of NPH and the lente insulins is their variability of effect. Despite attempts to achieve low, constant concentrations, these basal insulins still produce a peak.[11]

A related weakness is their large variability of absorption. It is estimated that 80% of the inconsistency of therapeutic effect of NPH is due to variability in absorption from the subcutaneous site.[19] At least four features of the available longer-acting insulins contribute to absorption variability. First, these insulins are in hexameric form. Once injected, the hexamers slowly dissociate into dimers and monomers, which are then absorbed into the tissue. The rate of dissociation and subsequent absorption is highly variable within and between subjects. Second, because they are suspensions, these insulins must be thoroughly mixed. If they are not, inhomogeneities can occur or insulin crystals can remain in the vials. Third, insulin injected as crystals in a suspension can be trapped in the tissue, unable to diffuse toward a capillary vessel, and may degrade over time.[5] Finally, variations in absorption may result from differences in local blood flow and tissue structure, resulting in a high intrapatient variability of effect when injected at different body sites.[20]

The excessive variability of absorption of NPH and lente insulins is associated with a high rate of hypoglycemia, the most common and severe complication of insulin therapy.[21] Nocturnal hypoglycemia is particularly common in patients with well-controlled type 1 diabetes.[22] Reducing the incidence of nocturnal hypoglycemia is of utmost importance given that even mild episodes of hypoglycemia can blunt counterregulatory hormonal responses and increase the risk of hypoglycemia unawareness.[22]

Recent attempts to produce better long-acting insulins have focused on insulin analogs. Whereas the extended action of NPH and lente insulins is produced by combining insulin with a retarding agent, insulin analogs are prepared by rearranging amino acids in the insulin molecule or attaching the insulin molecule to a side chain to attain desirable pharmacological attributes.

Long-Acting Insulin Analogs

Insulin analogs are similar in structure and function to regular human insulin, a

Table 1. Approximate Pharmacokinetic Parameters of Basal Human Insulins

Insulin	Onset of Action (h)	Peak Action (h)	Duration of Action (h)
NPH	1–2	5–7	13–18
Lente	1–3	4–8	13–20
Ultralente	2–4	8–14	18–30
[N-palmitoyl Lys (B29)]	1–3	4–6	13
Insulin glargine	1–5	N/A	24

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protein hormone comprising two polypeptide chains. The A and B chains of human insulin are 21 and 30 amino acids in length, respectively. The chemical, physical, and biological properties of insulin are determined by the sequence of these amino acids. Changing their sequence or extending the chains can alter the pharmacokinetic and pharmacodynamic profiles of the insulin.

Experience gained with existing long- and intermediate-acting insulins has informed the development of long-acting insulin analogs. Theoretically, an optimum basal insulin is one that could be administered once daily, would have peakless action, would be consistently absorbed, and would be associated with lower rates of hypoglycemia and better glucose control than currently available insulins.

To minimize the absorption problems associated with an insulin suspension, insulin analogs have been formulated as homogenous solutions so that they may be more evenly distributed and diffuse more readily at a capillary surface. One such soluble insulin is [Ne-palmitoyl Lys (B29)] human insulin.[19] Modification through fatty acid acylation of the insulin extends its duration of action by increasing the residence time at the site of injection, in the circulation, and in the interstitial space at target sites. However, preliminary investigation indicates that a four- to fivefold higher dose of [Ne-palmitoyl Lys (B29)] human insulin is needed to achieve a similar effect to NPH insulin. It is uncertain at this time whether differences in dosing are because of lower potency or decreased availability of [Ne-palmitoyl Lys (B29)] compared with NPH.[19]

Another strategy to prolong insulin absorption involves the substitution and/or addition of basic amino acid residues at locations on the A and B chains to elevate the isoelectric point of the insulin. When an acidic solution enters the neutral pH subcutaneous tissue, insulin molecules crystallize, retarding absorption of the insulin into the circulation.

The first long-acting insulin analog to use this mechanism was NovoSol Basal, which had a much slower absorption than human ultralente insulin. However, NovoSol Basal was associated with local inflammatory reactions and increasing dosing requirements. Therefore, development was discontinued.[12]

In addition to diminished potency and local site reactions, development of insulin analogs has been hampered by their potential to induce cell proliferation and carcinogenicity, which may be related to their ability to cross-react with insulin-like growth factor-1 (IGF-1). For this reason, all new insulin analogs are now tested for cross reactivity with IGF-1.

Promising long-acting insulin analogs, such as NN304 (Novo Nordisk, Princeton, NJ), are in the later stages of development. Recently, the Food and Drug Administration approved insulin glargine (Lantus, Aventis Pharmaceuticals, Bridgewater, NJ) for use in patients with type 1 or type 2 diabetes.

NN304

NN304 (ε-LysB29-myristoyl, des [B30] human insulin) is a long-acting insulin acylated with a 14-C-fatty acid chain, which allows prolonged action due to reversible binding to albumin.[23] In healthy subjects (n = 10), bioactivity of NN304 was ~70% lower than that of NPH. However, in a separate study with 16 healthy subjects, NN304 demonstrated an intrapatient variability of effect that was approximately half of that seen with NPH.[23] Clinical data in diabetic subjects should soon be available to indicate whether this insulin will offer significant benefits to diabetic patients.

Insulin glargine

Insulin glargine (HOE 901, 21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg human insulin) has shown significant benefits in preclinical glucose clamp studies and in clinical trials with type 1 and type 2 diabetic patients. Like NovoSol Basal, insulin glargine relies on shifting the isoelectric point of the insulin to a neutral pH (7.0).[5]

Insulin glargine is a homogenous solution, so it lacks some of the problems associated with insulin suspensions. Results of absorption studies in healthy volunteers and subjects with type 1 (Figure 1) and type 2 diabetes show that insulin glargine has a peakless, long-lasting action profile with more reproducible pharmacokinetics than NPH.[24–27] Additionally, no differences in absorp-

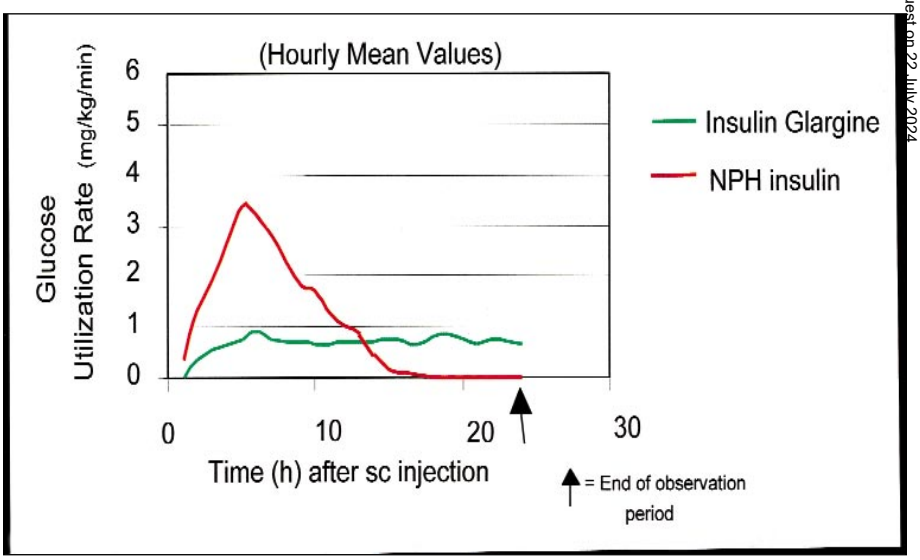

Figure 1. Time-action profile of insulin glargine and NPH human insulin in subjects with type 1 diabetes mellitus.[26]

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tion were observed when insulin glargine was injected at different body sites (leg, arm, or abdomen) in a crossover study with healthy volunteers.[28]

Short-term (4 weeks)[29–32] and long-term (28 weeks)[33,34] clinical safety and efficacy studies have been conducted comparing insulin glargine to NPH human insulin in both type 1 and type 2 diabetes. These studies have demonstrated that once-daily insulin glargine is as effective as or more effective than once- and twice-daily NPH regimens for glycemic control as measured by fasting plasma glucose and HbA_{1c}, in many cases with reduced incidence of nocturnal hypoglycemia.[29,32–34]

One drawback of insulin glargine compared with NPH and lente insulins is that it cannot be mixed with other insulins (e.g., lispro).[35]

Safety evaluations of insulin glargine indicate it is at least as safe as NPH; the frequency and types of adverse events in diabetic subjects are similar between treatments. Immunogenicity studies show no increased antibody development with insulin glargine compared with regular human insulin.[36] Furthermore, in vitro studies show that the IGF-1 receptor-mediated growth-promoting activity of insulin glargine in muscle cells is not different from that of native human insulin.[37]

Postmarketing data are needed to confirm the beneficial effects demonstrated by insulin glargine in controlled trials with diabetic subjects. The clinical benefits of insulin glargine must be established by improvement in overall patient outcomes as measured by glycemic control, incidence of hypoglycemia, and improved quality of life.[9]

Summary

A constant supply of low-level basal insulin is essential to improving overall glycemic control. Achieving adequate basal insulin substitution requires knowledge of the pharmacology and limitations of available insulins.

Advances in the development of new long-acting insulin analogs will expand therapeutic options in the near future, improving the health of patients with diabetes. Physician enthusiasm will be an important factor in acceptance of insulin therapy by type 2 diabetic patients.

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