An Evidence-Based Summary of Insulin Analogues

Bethany A. Fedutes, PharmD, Amy Calabrese Donihi, PharmD, BCPS, Colleen M. Culley, PharmD, BCPS, Bryan J. McCreery, PharmD Candidate, and Nicole T. Ansani, PharmD

Educational Objectives

- Compare and contrast the pharmacokinetic and pharmacodynamic parameters of the newer insulin analogues and existing human insulin products.
- Describe the efficacy and safety outcomes of the insulin analogues versus comparative agents in key clinical trials.
- Provide recommendations for an optimal therapeutic insulin regimen using evidence-based medicine and patient clinical presentations.

Abstract

The novel insulin analogues—insulin lispro, insulin aspart, and insulin glargine—are alternatives to human insulin products. Clinical trials have demonstrated equal or superior efficacy and safety outcomes when these analogues are compared with human insulin, particularly because of a lower incidence of hypoglycemic events. Because the analogues are more expensive than human insulin, it is recommended that they be used as alternatives for patients who cannot achieve tight blood glucose control with adequately dosed human insulin, for patients who have continued hypoglycemic or other intolerable events, and for patients just starting insulin therapy.

Introduction

Diabetes mellitus (DM) is a chronic disease, affecting more than 16 million Americans. The consequences of diabetes, such as microvascular and macrovascular complications, are frequently encountered. In 1997, the economic impact of DM and the associated complications was more than $44 billion in direct expenditures and above $54 billion in indirect medical expenditures.

In 2002, the American Diabetes Association (ADA) estimated medical expenditures and lost productivity associated with DM to be $132 billion. Also in that year, per capita medical expenditures totaled $13,243 for individuals with DM. These costs are expected to increase in future years as a result of the growing obesity epidemic, the increasing prevalence of diabetes, and the rising costs of health care services.

Landmark reports, such as the Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective Diabetes Study (UKPDS), and the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, have shown that intensive insulin treatment with strict glycemic control results in significant reductions in both microvascular and macrovascular complications. These regimens, however, involve multiple injections of insulin and multiple fingerstick blood draws for glucose monitoring each day. Further, patients with DM often take several other medications for other underlying comorbidities, such as hypertension and dyslipidemia. Therefore, patients who need good glucose control must often follow medication regimens that are complicated and difficult to manage.

Proper nutrition, exercise, and education are the cornerstones of DM therapy. Medication is an integral part of treatment, and the choices of insulin products have increased over the past few years. As therapeutic decisions pose challenges for prescribers, patients are also faced with difficulties in understanding their insulin regimens.
In this article, we review, compare, and contrast the newer insulin analogues with the existing human insulin products to help guide clinicians in optimal insulin management.

Pharmacology

Endogenous human insulin is a 51-amino acid protein consisting of two peptide chains that are synthesized and secreted by the pancreatic beta cells. Structural alterations of this sequence, prepared by recombinant DNA (rDNA) technology, allow for the production of synthetic insulin analogues, such as rapidly acting insulin lispro (Humalog®, Eli Lilly) and insulin aspart (NovoLog®, NovoNordisk) and long-acting insulin glargine (Lantus®, Aventis).

The primary action of insulin is the regulation of glucose metabolism. Insulin and the insulin analogues stimulate peripheral glucose uptake, primarily by skeletal muscle and fat, inhibiting hepatic glucose production, thereby lowering blood glucose concentrations. Insulin inhibits lipolysis (in the adipocytes) and proteolysis, enhancing protein synthesis. All the beta chain at positions B28 and B29 is reversed. Similarly, insulin in that the natural sequence of amino acids located on replacement of proline at position B28 with aspartic acid. Insulin aspart differs structurally from human insulin by the sequence, prepared by recombinant DNA (rDNA) technology, allow for the production of synthetic insulin analogues, such as rapidly acting insulin lispro (Humalog®, Eli Lilly) and insulin aspart (NovoLog®, NovoNordisk) and long-acting insulin glargine (Lantus®, Aventis).

These amino acid transpositions and replacements result in decreased hexameric binding following SQ injection, more rapid absorption and onset of action, and a shorter duration of action compared with endogenous human insulin.

The structure of insulin glargine is similar to that of endogenous human insulin, with two modifications: the addition of positive charges (two arginine molecules to the C-terminus of the beta chain) and the replacement of asparagine at position A21 with glycine. Using a SQ injection, this structural chain neutralizes the acidic insulin glargine solution and forms microprecipitates from which small amounts of insulin are released. The addition of zinc stabilizes the structure of insulin hexamers (i.e., it delays disassociation into monomers) and extends the duration of action by reducing the absorption rate from the injection site, leading to an overall delayed absorption and prolonged duration of action.

Pharmacokinetics and Pharmacodynamics

Studies evaluating the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of the various insulin products are inconsistent with respect to definitions, methodology, and patient populations. Consequently, wide differences exist in published tables designed to summarize the time–activity properties of the insulin products.

Compared with regular human insulin, both rapidly acting insulin analogues (aspart and lispro) reach peak plasma concentrations that are higher and occur earlier, leading to a faster onset of blood glucose-lowering action (Table 1). Insulin analogues also exhibit a shorter duration of action. Some PK and PD studies directly comparing insulin aspart and lispro show similar clinical properties.

In PK/PD comparisons of insulin glargine, NPH insulin, and ultralente insulin, insulin glargine exhibits a more prolonged absorption and a relatively constant concentration–time profile with no pronounced peak.

Table 1 presents the results of a study that compared glargine, NPH, and ultralente in 20 patients with type-1 DM.

**Table 1**  Comparison of the Pharmacokinetic and Pharmacodynamic Properties of Various Intermediate and Long-Acting Insulin Products in Type-1 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Insulin Product</th>
<th>Dose (units/kg)</th>
<th>Onset (minutes)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (microunit/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (minutes)</th>
<th>Duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular human insulin</td>
<td>0.1–0.4</td>
<td>30–45</td>
<td>51</td>
<td>50–120</td>
<td>5</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>0.1–0.4</td>
<td>0–15</td>
<td>116</td>
<td>30–90</td>
<td>3</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>0.15</td>
<td>0–15</td>
<td>82.1</td>
<td>40–50</td>
<td>3–5</td>
</tr>
<tr>
<td>Human insulin (NPH)</td>
<td>0.3</td>
<td>60–120&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22.8 ± 2.2</td>
<td>360–720</td>
<td>13.2 ± 2.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Human insulin ultralente</td>
<td>0.3</td>
<td>240–360&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25.9 ± 2.1</td>
<td>960–1,080</td>
<td>19 ± 5.8</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>0.3</td>
<td>1.5 ± 0.3</td>
<td>18.9 ± 0.3</td>
<td>(plateau between 3 and 24 hours)</td>
<td>20.5 ± 3.7</td>
</tr>
</tbody>
</table>

C<sub>max</sub> = maximum concentration; T<sub>max</sub> = time to maximum concentration.

*P < .05 versus insulin glargine.

Comparative studies of insulin analogues in both type-1 and type-2 DM have primarily evaluated fasting blood glucose and glycosylated hemoglobin (HbA1c) values against their human insulin counterparts. The following section briefly summarizes the clinical data for insulin aspart, lispro, and glargine in the key trials.

Readers should be cautious in interpreting subjective patient measures, such as satisfaction with insulin regimens and reports of adverse drug effects (ADEs) because of the lack of blinding in the studies. Blinding was not possible in most of the clinical trials because of (1) differences in administration time with regard to meals, (2) the appearance of the analogues, and (3) the mixing techniques for the analogues.

**Insulin Aspart**

In trials comparing insulin aspart with regular human insulin evaluated plasma glucose excursion and HbA1c control, insulin aspart consistently demonstrated lower plasma glucose excursion outside a predefined range (5.6–7.8 mmol/liter [100.8–140.4 mg/dl]) and improved HbA1c. Insulin aspart and regular human insulin were associated with a similar incidence of hypoglycemia.

Four additional trials (Table 2) of type-1 DM patients compared insulin aspart with regular human insulin with basal NPH insulin administration in both groups; the primary difference between these studies was an open-label design. Similar endpoints were evaluated with the addition of quality-of-life assessments. As noted in the blinded studies, there were significant improvements in HbA1c, plasma glucose excursion (determined by postprandial blood glucose), and quality-of-life assessment with insulin aspart compared with regular human insulin. However, higher doses of NPH insulin were required with insulin aspart than with regular human insulin.

Other comparative studies of insulin aspart in the type-2 diabetic patients revealed similar efficacy with regular human insulin, illustrated by a lack of any difference in plasma glucose excursion, HbA1c, and blood glucose levels. In addition, a similar incidence of hypoglycemia was noted.

Finally, insulin aspart was compared with regular human insulin and insulin lispro via administration by a continuous SQ insulin infusion (CSII). The primary endpoints evaluated HbA1c, serum fructosamine, blood glucose profiles, and insulin dose. Safety endpoints were the incidence of hypoglycemia, hyperglycemia, and ADEs. Similar efficacy and safety results were seen with all three products.

**Insulin Lispro**

The relative efficacy and safety of insulin lispro and regular human insulin with basal administration of NPH insulin in each group have been evaluated in type-1 diabetic patients. As in the insulin aspart trials, primary endpoints included plasma glucose excursion, HbA1c, NPH insulin dose, and hypoglycemia. Significant improvements in plasma glucose excursions were demonstrated with insulin lispro, compared with regular human insulin, but overall glucose control (HbA1c) was similar. Safety reports show a consistent decrease in nocturnal hypoglycemia with insulin lispro.

The overall incidence of hypoglycemia was similar or improved with insulin lispro compared with regular human insulin. A meta-analysis examined the pooled incidence of hypoglycemia in clinical trials with insulin lispro. Although the incidence of severe hypoglycemic events was similar in the individual studies, increasing the power analysis (thus increasing the ability to determine a statistical difference if one exists) demonstrated a significantly lower incidence of hypoglycemia with insulin lispro than with regular human insulin.
A similar comparative study was conducted in patients with type-2 DM. Outcomes assessed were serum blood glucose, HbA1c, cholesterol, and the occurrence of hypoglycemic events. The efficacy of insulin lispro was superior to regular human insulin in decreasing postprandial blood glucose at one and two hours after administration. The mean rate of hypoglycemic events was also significantly decreased in the insulin lispro patients compared with the patients receiving regular human insulin. No differences were reported between the groups in HbA1c, weight, insulin dose, or lipid parameters.

### Insulin Glargine

Trials have evaluated the efficacy and safety of insulin glargine and NPH insulin in type-1 DM patients (Table 4). Efficacy was commonly assessed by fasting plasma glucose levels and HbA1c; safety analyses focused on the incidence of hypoglycemia. In contrast to NPH insulin, insulin glargine consistently and significantly decreased fasting blood glucose and showed similar or superior overall glycemic control, as measured by HbA1c. The incidence of nocturnal hypoglycemia was also reduced with insulin glargine, although overall hypoglycemic control

---

**Table 3 Summary of Key Clinical Trials of Insulin Lispro in Type-1 Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methodology</th>
<th>Regimen</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holleman et al., 1997 (^{36}) (n = 199)</td>
<td>R, OL, MC, CO</td>
<td>IL = 0 minutes a.c. Hl = 30 minutes a.c. + basal NPH</td>
<td>(\bigtriangleup) (\bigtriangleup) ↓ ↓</td>
</tr>
<tr>
<td>Heller et al., 1998 (^{37}) (n = 135)</td>
<td>R, OL, MC, CO</td>
<td>IL = 0 minutes a.c. Hl = 30 minutes a.c. + basal NPH</td>
<td>(\bigtriangleup) ↓ ↓ ↓</td>
</tr>
<tr>
<td>Anderson et al., 1997 (^{38}) (n = 1,008)</td>
<td>R, OL, MC, CO</td>
<td>IL = 0 minutes a.c. Hl = 30–45 minutes a.c. + basal NPH</td>
<td>(\bigtriangleup) ↓ ↓ ↓</td>
</tr>
<tr>
<td>UK Trial Group, 2001 (^{39}) (n = 423)</td>
<td>R, OL, MC</td>
<td>IL = a.c. Hl = a.c.</td>
<td>(\bigtriangleup) ↓ ↓ ↓</td>
</tr>
</tbody>
</table>

- \(\bigtriangleup\) = significant improvement with insulin lispro compared with regular human insulin; \(\bigtriangledown\) = no difference.
- Key: \(\bigtriangleup\) = significant improvement with insulin lispro compared with regular human insulin; \(\bigtriangledown\) = no difference.
- Note: Results are not reported in cells without data.

**Table 4 Summary of Key Clinical Trials of Insulin Glargine in Type-1 Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methodology</th>
<th>Regimen</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pieber et al., 2000 (^{42}) (n = 333)</td>
<td>R, OL, MC</td>
<td>IG30 = h.s. NPH = h.s./b.i.d. + a.c. HI</td>
<td>(\bigtriangleup) ↓</td>
</tr>
<tr>
<td>Rosenstock et al., 2000 (^{43}) (n = 256)</td>
<td>R, OL, MC</td>
<td>IG80 = h.s. NPH = h.s./b.i.d. + a.c. HI</td>
<td>(\bigtriangledown) ↓ ↓ ↓ ↓</td>
</tr>
<tr>
<td>Ratner et al., 2000 (^{44}) (n = 524)</td>
<td>R, OL, MC</td>
<td>IG = h.s. NPH = h.s./b.i.d. + a.c. HI</td>
<td>(\bigtriangleup) ↓ ↓ ↓ ↓</td>
</tr>
<tr>
<td>Raskin et al., 2000 (^{45}) (n = 619)</td>
<td>R, OL, MC</td>
<td>IG = h.s. NPH = h.s./b.i.d. + a.c. HI</td>
<td>(\bigtriangledown) ↓ ↓ ↓ ↓</td>
</tr>
<tr>
<td>Rossetti et al., 2003 (^{46}) (n = 51)</td>
<td>R, OL, SC</td>
<td>IG = h.s./dinner NPH = q.i.d. + a.c. IL</td>
<td>(\bigtriangleup) ↓ ↓ ↓ ↓</td>
</tr>
<tr>
<td>Leport et al., 2003 (^{47}) (n = 32)</td>
<td>R, OL, SC</td>
<td>IG = h.s./dinner CSII (IL)</td>
<td>(\bigtriangleup) ↓ ↓ ↓ ↓</td>
</tr>
</tbody>
</table>

- \(\bigtriangleup\) = significant improvement with insulin glargine compared with NPH; \(\bigtriangledown\) = significant improvement with NPH compared with insulin glargine; \(\bigtriangledown\) = no difference.
- Key: \(\bigtriangleup\) = significant improvement with insulin glargine compared with NPH; \(\bigtriangledown\) = significant improvement with NPH compared with insulin glargine; \(\bigtriangledown\) = no difference.
- Note: Results are not reported in cells without data.
Similar study designs and study outcomes were employed to evaluate insulin glargine and NPH insulin in type-2 diabetic patients. Overall, no significant differences in efficacy were seen with either product. Similar to the findings in the type-1 DM population, significant decreases in nocturnal hypoglycemia were commonly reported, but the overall incidence of hypoglycemia was similar between agents (Table 5).

### Drug Interactions

As with other insulin products, insulin analogue requirements may be increased by other medications, such as corticosteroids, isoniazid, niacin, estrogen, phenothiazines, and thyroid replacement therapy. Furthermore, reductions in insulin requirements may be necessary with the concomitant use of oral hypoglycemic agents, salicylates, sulfa antibiotics, monoamine oxidase (MAO) inhibitors, angiotensin-converting enzyme (ACE)-inhibitors, and alcohol.9–11

### Adverse Drug Events

Hypoglycemia is the most common ADE associated with insulin therapy, and this effect is a primary concern of diabetes management.53 Rapid-acting insulin analogues were developed and marketed to decrease the incidence of hypoglycemia between meals by their shorter duration of action.53 These analogues decrease blood glucose levels more quickly than regular human insulin does, although a consistent decrease in the incidence of hypoglycemia has not been demonstrated.53

Trials comparing insulin lispro and regular human insulin have shown decreases in overall hypoglycemia with insulin lispro in type-136–40 and in type-241 DM patients. This overall decrease is attributed primarily to a significant decrease in nocturnal hypoglycemia.36,53 Because of the rapid onset with insulin lispro, hypoglycemia occurs earlier following meals, compared with regular human insulin.33

Studies comparing insulin aspart and regular human insulin have generally shown similarities in the incidence of hypoglycemia, except for two trials in which insulin aspart decreased only major hypoglycemia (defined as needing third-party help or administration of parenteral glucose or glucagons).28,29 A comparison of insulin aspart, insulin lispro, and regular human insulin (administered by SQ infusion via a pump in patients with type-1 DM) showed that more than 90% of patients in all groups reported at least one minor hypoglycemic event (defined as a symptom of hypoglycemia confirmed by a blood glucose meter reading below 50 mg/dl with the patient able to treat the event unaided), with overall similarities in hypoglycemia type and incidence.35 To date, no studies have compared the incidence of hypoglycemia with insulin aspart or lispro when used as an intermittent SQ injection.

In comparisons of insulin glargine and NPH insulin in more than 5,000 patients with type-1 or type-2 DM, the incidence of hypoglycemia was similar between agents;54 however, significant decreases in nocturnal hypoglycemia were noted with insulin glargine.48–50

Other commonly reported ADEs resulting from insulin therapy include allergic reactions, injection-site reactions, lipoatrophy, pruritus, and rash.1,11 In some studies, the incidence of these events was similar for insulin aspart or lispro when compared with regular human insulin.1,2

A higher incidence of injection-site reactions was reported with insulin glargine (2.7%) than with NPH insulin (0.7%).11

---

Table 5  **Summary of Key Clinical Trials of Insulin Glargine in Type-2 Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yki-Jarvinen et al., 2000* (n = 426)</td>
<td>R, OL, MC</td>
</tr>
<tr>
<td>Rosenstock et al., 2001† (n = 518)</td>
<td>R, OL, MC</td>
</tr>
<tr>
<td>Massi Bemedetto et al., 2003§ (n = 578)</td>
<td>R, OL, MC</td>
</tr>
<tr>
<td>Raskin et al., 1998* (n = 157)</td>
<td>R, OL, MC</td>
</tr>
<tr>
<td>Matthews et al., 1998* (n = 204)</td>
<td>R, OL, MC</td>
</tr>
</tbody>
</table>

**Regimen**

| IG = h.s. + oral agents | IG = h.s. + oral agents | IG = h.s. + oral agents | IG30 = h.s. + oral agents |
| NPH = h.s. + oral agents | NPH = h.s. + oral agents | NPH = h.s. + oral agents | NPH = h.s. + oral agents |

- **Result**
  - HbA1C
  - Fasting blood glucose
  - Hypoglycemia
  - Nocturnal hypoglycemia

  a.c. = before meals; b.i.d. = twice daily; HbA1C = glycosylated hemoglobin; HI = regular human insulin; h.s. = at bedtime; IG = insulin glargine; IG30 = insulin glargine containing 30 mcg/ml of zinc; IG80 = insulin glargine containing 80 mcg/ml of zinc; MC = multicenter; OL = open label; R = randomized; SC = single center.

  Key: ↓ = significant improvement with insulin glargine compared with NPH; ⌀ = no difference.

  Note: Results are not reported in cells without data.

  * Available only in Abstract form.

---

References:

1. Yki-Jarvinen et al., 2000
2. Rosenstock et al., 2001
3. Massi Bemedetto et al., 2003
4. Raskin et al., 1998
5. Matthews et al., 1998

Table 5  **Summary of Key Clinical Trials of Insulin Glargine in Type-2 Diabetes Mellitus**
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Dosage Form</th>
<th>Drugstore.com Price or ($/unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% human insulin isophane suspension</td>
<td>Humulin® 50/50</td>
<td>100 units/10-ml vial</td>
<td>$25.88</td>
</tr>
<tr>
<td>[NPH]/50% human insulin injection</td>
<td>(Eli Lilly)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[buffered regular]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% human insulin isophane suspension</td>
<td>Humulin® 70/30</td>
<td>70/30 in 3-ml pen</td>
<td>$161.29/10</td>
</tr>
<tr>
<td>[NPH]/30% human insulin injection</td>
<td></td>
<td>100 units/1.5-ml cartridge</td>
<td>$34.99/5</td>
</tr>
<tr>
<td>[buffered regular]</td>
<td></td>
<td>100 units/10-ml vial</td>
<td>$29.52</td>
</tr>
<tr>
<td>Novolin® 70/30</td>
<td></td>
<td>100 units/1.5-ml syringe</td>
<td>$41.99/5</td>
</tr>
<tr>
<td>(Novo Nordisk)</td>
<td></td>
<td>100 units/1.5-ml cartridge</td>
<td>$33.99/5</td>
</tr>
<tr>
<td>100 units/10-ml vial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 units/3-ml PenFill® cartridge</td>
<td></td>
<td></td>
<td>$82.60/5</td>
</tr>
<tr>
<td>Human insulin lente</td>
<td>Humulin® L</td>
<td>100 units/10-ml vial</td>
<td>$28.42</td>
</tr>
<tr>
<td></td>
<td>Novolin® L</td>
<td>100 units/10-ml vial</td>
<td>$25.88</td>
</tr>
<tr>
<td>Human insulin NPH</td>
<td>Humulin® N</td>
<td>100 units/10-ml vial</td>
<td>$28.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 units/3-ml pen</td>
<td>$76.28/5</td>
</tr>
<tr>
<td>Novolin® N</td>
<td></td>
<td>100 units/1.5-ml syringe</td>
<td>$40.85/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 units/1.5-ml cartridge</td>
<td>$38.59/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 units/10-ml vial</td>
<td>$28.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 units/ml 3-ml Innolet syringe</td>
<td>$55.01/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 units/ml 3-ml pen cartridge</td>
<td>$75.81/5</td>
</tr>
<tr>
<td>Human insulin regular</td>
<td>Humulin® R</td>
<td>100 units/10-ml vial</td>
<td>$28.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 units/1.5-ml cartridge</td>
<td>$34.99/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 units/20-ml vial</td>
<td>$184.83</td>
</tr>
<tr>
<td>Novolin® R</td>
<td></td>
<td>1.5-ml syringe</td>
<td>$35.99/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.5-ml cartridge</td>
<td>$37.99/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-ml vial</td>
<td>$28.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-ml PenFill® cartridge</td>
<td>$75.81/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Innolet 15 ml</td>
<td>$54.97</td>
</tr>
<tr>
<td>Human insulin ultralente</td>
<td>Humulin® U</td>
<td>100 units/10-ml vial</td>
<td>$28.42</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>NovoLog®</td>
<td>100 units/10-ml vial</td>
<td>$65.46</td>
</tr>
<tr>
<td>(Novo Nordisk)</td>
<td></td>
<td>3-ml FlexPen® syringe</td>
<td>$119.90/5</td>
</tr>
<tr>
<td>Insulin aspart 30%/insulin aspart protamine</td>
<td>NovoLog® 70/30</td>
<td>3-ml FlexPen® syringe</td>
<td>$128.31/5</td>
</tr>
<tr>
<td>70%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Lantus® (Aventis)</td>
<td>100 units/10-ml vial</td>
<td>$46.99</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>Humalog®</td>
<td>100 units/ml 1.5-ml cartridge</td>
<td>$55.58/5</td>
</tr>
<tr>
<td>(Eli Lilly)</td>
<td></td>
<td>100 units/10-ml vial</td>
<td>$55.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 units/3-ml pen cartridge</td>
<td>$122.07/5</td>
</tr>
<tr>
<td>75% insulin lispro protamine suspension</td>
<td>Humalog® 75/25</td>
<td>75/25/20-ml vial</td>
<td>$123.68</td>
</tr>
<tr>
<td>25% insulin lispro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% insulin lispro protamine/50% insulin lispro</td>
<td>Humalog® 50/50</td>
<td>100 units/vial</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Data from Drugstore.com.59
This increase may be attributed to the pH and PK parameters of insulin glargine.

Weight gain has been less commonly reported with insulin glargine than with NPH insulin. The incidence of all other events was similar with these two products.

A greater incidence of three-step progression, as assessed by the Early Treatment Diabetic Retinopathy Scale (ETDRS)—the gold standard for grading the severity of diabetic retinopathy in trials—over six months via fundus photography was seen with insulin glargine (7.5%) compared with NPH insulin (2.7%).

The manufacturer of insulin glargine, Aventis Pharmaceuticals, stated that the overall relevance of this ADE could not be determined because of the small sample, the short duration of follow-up, and a lack of consistent findings. An independent panel convened by Aventis concluded that this finding was not related to treatment with insulin glargine. However, the FDA mandated a phase 4 study to compare the ETDRS with insulin glargine and NPH insulin. A final report is anticipated in April 2005.

Further studies are being conducted to determine the effects of insulin glargine on the progression of retinopathy and the incidence of mitogenicity compared with NPH human insulin.

**Dosage and Administration**

As with other insulin products, the dosage regimens of the analogues vary among patients and should be individualized to address patients’ specific metabolic needs, eating habits, and lifestyles. The injection sites should be rotated within the same region.

When used as a mealtime therapy, insulin aspart and lispro should be given immediately before—or, at the most, 15 minutes before—a meal.

Insulin aspart or lispro may be mixed with NPH and ultralente insulin if the rapidly acting analogue is drawn into the syringe first and the injection is given immediately after mixing. Clinical data support the administration of insulin aspart or lispro by SQ infusion via a pump in the abdominal wall; however, only insulin aspart has gained FDA approval for this use. Infusion sets and the insulin in the sets must be changed every 48 hours or sooner to ensure the activity of the insulin and proper pump function.

Insulin glargine is given by SQ injection once daily in the abdomen, thigh, or deltoid areas. This product is not for intravenous use, and it must not be diluted or mixed with any other insulin or solution because of the potential for alteration of the PK or PD properties of the insulin glargine or mixed insulin.

In insulin-naïve patients who have already been treated with oral hypoglycemic agents, the average starting dose of insulin glargine in trials is 10 units once daily. The dose should be adjusted according to the patient’s needs (range, 2–100 units).

In patients who are already taking intermediate-acting or long-acting insulin once daily, the dose of insulin glargine is the same total dose, administered once daily at bedtime. When patients are switched from twice-daily NPH insulin to insulin glargine once daily at bedtime, the dose of insulin glargine should be reduced by approximately 20% (compared to total daily units of NPH insulin) within the first week of treatment and then adjusted based on patient response. The amount and timing of short-acting insulin or oral hypoglycemic agents may need to be adjusted.

**Cost**

As mentioned earlier, studies have shown similar or superior efficacy and safety outcomes with the newer insulin analogues, which may potentially decrease direct and indirect costs associated with DM. However, few pharmacoeconomic studies evaluating the use of the insulin analogues are available to compare the overall cost of therapy in clinical practice.

A willingness-to-pay evaluation of insulin lispro, compared with regular human insulin therapy, revealed that patients consider the benefits of insulin lispro treatment sufficient to justify the higher price. In addition, a pharmacy and medical claims data analysis, in which all-cause average health care utilization and costs over 12 months were evaluated by type of service, demonstrated cost-neutrality with the administration of insulin lispro, compared with regular human insulin, in 1,832 subject-pairs. Although patients using insulin lispro made more office visits and had more prescriptions than patients using regular human insulin, they experienced significantly fewer inpatient and hypoglycemia-related hospitalizations. Furthermore, the insulin lispro subjects had more office visit expenses ($106) and pharmacy charges ($477) over one year. In contrast, they had significantly lower inpatient hospital expenditures than patients using regular human insulin. The differences in costs may have contributed to an overall savings, although not significant, with insulin lispro ($216) during the 12-month evaluation period.

Insulin glargine is more expensive than NPH; no pharmacoeconomic studies are available to evaluate the overall cost of care.

Table 6 presents a comparison of insulin products based on purchase data obtained from an Internet pharmacy. These prices more closely reflect the actual expense to a patient without insurance coverage.

**Clinical Application of Evidence**

The data suggest that short-acting insulin analogues are viable options for patients who have not responded to or who are intolerant of regular human insulin. The newer short-acting analogues have shown a lower incidence of hypoglycemic events, compared with regular human insulin, with similar, if not superior, control of HbA1c and postprandial blood glucose levels for both type-1 and type-2 DM patients. Because of their convenience in dosing regimens, short-acting analogues may also be an alternative for patients who need a flexible timing schedule for pre-meal insulin administration.

Clinical data demonstrate that insulin glargine is associated with a similar or lower rate of hypoglycemic events with similar or improved glucose control. Patients presenting with continuous nocturnal hypoglycemia who are not meeting HbA1c targets may benefit from a nighttime dose of insulin glargine. However, patients should be closely monitored for nocturnal hypoglycemia, and the dose of insulin glargine may need to be reduced if symptoms are observed. Insulin glargine is also available in an intravenous formulation for use in the hospital setting, providing another option for patients who cannot take insulin by SQ injection.
goals with NPH insulin are appropriate candidates for insulin glargine therapy. In addition, because of the PK properties of glargine, producing peakless insulin coverage, this agent is also recommended for patients newly initiated with intermediate or long-acting insulin therapy.

As a result of the increased cost of the analogues, it is not recommended that patients who are stabilized and achieving goals with regular or NPH insulin be switched to a different therapy. However, these new agents present promising alternatives in patients who are intolerant of regular or NPH insulin, who have experienced continual hypoglycemia, who have not achieved tight control of glucose levels, and who are just beginning insulin therapy.

Future and Newly Introduced Therapies

Multiple daily insulin injections may be necessary for patients to achieve tight blood glucose control. Alternative, noninvasive routes of administration are being explored to provide for more convenient insulin delivery. At this time, the focus has been on the pulmonary administration of insulin because of the potential success demonstrated in early clinical trials. Two products, Exubera® (Aventis/Pfizer/Nektar Therapeutics) and AERx® iDMS (Aradigm Co./Novo Nordisk), are inhaled insulin formulations and are being studied for the treatment of type-1 and type-2 DM in phase 3 trials.

In addition to the pulmonary route of administration, several oral insulin dosage forms are under investigation: (1) an oral crystalline capsule (Lilly/Autoimmune), in phase 2; (2) a conjugated oral insulin product hexyl-insulin-monoconjugate-2 (Nobex Corporation), in phase 2; and (3) an aerosolized liquid (oral spray) formulation for buccal administration (Oralin™, Generex Biotechnology), phase not disclosed.

An insulin dermal patch (Altea Therapeutics) is also in phase 1 of development. Novo Nordisk has filed New Drug Applications (NDAs) with the FDA for insulin detemir (Levemir™), phase not disclosed.

An insulin dermal patch (Altea Therapeutics) is also in phase 1 of development. Novo Nordisk has filed New Drug Applications (NDAs) with the FDA for insulin detemir (Levemir™), phase not disclosed.

An insulin dermal patch (Altea Therapeutics) is also in phase 1 of development. Novo Nordisk has filed New Drug Applications (NDAs) with the FDA for insulin detemir (Levemir™), phase not disclosed.

An insulin dermal patch (Altea Therapeutics) is also in phase 1 of development. Novo Nordisk has filed New Drug Applications (NDAs) with the FDA for insulin detemir (Levemir™), phase not disclosed.

An insulin dermal patch (Altea Therapeutics) is also in phase 1 of development. Novo Nordisk has filed New Drug Applications (NDAs) with the FDA for insulin detemir (Levemir™), phase not disclosed.

An insulin dermal patch (Altea Therapeutics) is also in phase 1 of development. Novo Nordisk has filed New Drug Applications (NDAs) with the FDA for insulin detemir (Levemir™), phase not disclosed.

An insulin dermal patch (Altea Therapeutics) is also in phase 1 of development. Novo Nordisk has filed New Drug Applications (NDAs) with the FDA for insulin detemir (Levemir™), phase not disclosed.

Conclusion

Intensive insulin therapy has documented benefits in reducing microvascular and macrovascular complications associated with DM. Currently available insulin formulations include rapid-acting, short-acting, intermediate and long-acting, and mixed insulin products. Insulin aspart and lispro have shown equal, if not superior, efficacy and safety compared with regular human insulin. Insulin glargine has reported efficacy and safety superior to NPH insulin, mainly as a consequence of its peakless PK profile that closely mimics human basal insulin secretion. Fewer hypoglycemic events have been noted, and these agents are associated with dosing convenience and improved patient satisfaction.

References


47. Lepore G, Dodesini AR, Nosari I, Trevisan R. Both continuous subcutaneous insulin infusion with a multiple daily insulin injection regimen with glargine as basal insulin are equally better than traditional multiple daily insulin injection treatment. Diabetes Care 2003;26:1321–1322.


Disclosure
Dr. Ansani has disclosed the following relationships:
Current: Employee of Pfizer. Formerly: Consultant, Eli Lilly, Speakers Bureau: Pfizer; Sanofi-Synthelabo.
Dr. Fedutes, Dr. Donihi, Dr. Culley, and Mr. McCreney have indicated no relationships to disclose.
Continuing Education for Physicians and Pharmacists

*P&T®* 2005;30(2):112–120
ACPE Program #079-999-05-014-H01
Expiration Date: February 28, 2006

**TOPIC: An Evidence-Based Summary of Insulin Analogues**

---

**CME Accreditation**

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Jefferson Medical College and MediMedia USA, Inc.

Jefferson Medical College of Thomas Jefferson University, as a member of the Consortium for Academic Continuing Medical Education, is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. All faculty/authors participating in continuing medical education activities sponsored by Jefferson Medical College are expected to disclose to the activity audience any real or apparent conflict(s) of interest related to the content of their article(s). Full disclosure of these relationships appears on the last page of the article.

---

**Continuing Medical Education Credit**

This CME activity is designed to assist physicians and other health care professionals who are P&T committee members in making formulary decisions. Its goal is to increase participants’ ability to recognize and treat important medical problems.

Jefferson Medical College designates this continuing medical education activity for a maximum of one Category 1 credit toward the Physician’s Recognition Award (PRA) of the American Medical Association. Each physician should claim only those credits that he/she actually spent in the educational activity.

This credit is available for the period of one year from the date of publication.

Although forms will be processed when received, certificates for CME credits will be issued every six months, in February and August. Interim requests for certificates can be made by contacting the Jefferson Office of Continuing Medical Education at (215) 955-6992 or by going online to [http://jeffline.tju.edu/jeffcme/](http://jeffline.tju.edu/jeffcme/).

---

**Continuing Pharmacy Education Credit**

The Department of Health Policy, Jefferson Medical College, is approved by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmaceutical education and complies with the Criteria for Quality for continuing pharmaceutical education programming. This program (079-999-05-014-H01) is acceptable for 1.0 hour of continuing education credit (0.1 CEUs) in states that recognize ACPE-approved providers. Statements of Credit indicating hours/CEUs will be mailed within six to eight weeks to participants who completed this activity and submitted a completed evaluation with payment.

---

**How to Apply for CE Credit**

1. Each CE article is prefaced by learning objectives for participants to use to determine whether the article relates to their individual learning needs.
2. Read the article carefully, paying particular attention to the tables and other illustrative materials.
3. Complete the questions and fill in the answers on the evaluation form on the next page.
4. Complete the CE Registration and Evaluation Form. Type or print your full name and address in the space provided, and evaluate the activity as requested. In order for the form to be processed, all information must be complete and legible.
5. Payment of $10 per exam is required for processing and maintenance of records. Make checks payable to *P&T®*. This processing fee is non-refundable.
6. Send the completed form, answer sheet, and $10 payment to:
   - Department of Health Policy
   - Jefferson Medical College
   - Attn: Continuing Education Credit
   - 1015 Walnut Street, Suite 115
   - Philadelphia, PA 19107

7. Be sure to mail the Registration, Evaluation Form, and $10 payment within one year of the date of publication. After that date, this article will no longer be designated for credit and forms cannot be processed.
Continuing Education Examination for Physicians and Pharmacists

TOPIC: An Evidence-Based Summary of Insulin Analogues

ACPE Program #079-999-05-014-H01

CE Evaluation: Select the one best answer to each of the following questions, and record your response on the examination answer sheet. Complete the additional requested information. Forward the answer sheet, with appropriate payment, to the Department of Health Policy, Jefferson Medical College, at the address indicated. A certificate of completion will be mailed within six to eight weeks of receipt of your exam/payment. (A minimum test score of 70% is required.)

Multiple Choice

Select the one correct answer:

1. All the following statements regarding insulin analogues are true except:
   a. Insulin analogues are created by slightly altering the amino acid sequence of endogenous human insulin.
   b. Insulin aspart is approved by the FDA for use in external subcutaneous insulin infusion pumps.
   c. Insulin glargine is a rapidly acting insulin.
   d. Insulin lispro is the only FDA-approved insulin for use in combination with a sulfonylurea.

2. Compared with regular human insulin, rapid-acting insulin analogues lispro and aspart:
   a. reach peak plasma concentrations that are higher and earlier.
   b. lead to a faster onset of blood glucose-lowering action.
   c. have a shorter duration of action.
   d. all of the above.

3. Comparative studies of insulin lispro and regular human insulin show that insulin lispro has:
   a. better overall glucose control (HbA1c).
   b. a consistent decrease in the occurrence of nocturnal hypoglycemia in patients with type-1 diabetes.
   c. worse efficacy in decreasing postprandial blood glucose in patients with type-2 diabetes.
   d. a similar mean rate of hypoglycemic events in type-2 diabetic patients.

4. In type-1 diabetic patients, comparisons of NPH and insulin glargine in clinical trials yield all of the following except:
   a. Insulin glargine consistently and significantly decreases fasting blood glucose.
   b. Insulin glargine shows similar or superior overall glycemic control.
   c. Overall glycemic control appears to worsen with insulin glargine than with NPH insulin.
   d. The incidence of nocturnal hypoglycemia is commonly reduced with insulin glargine.

5. A reduction in the amount of insulin prescribed may be necessary in individuals who are also taking:
   a. corticosteroids.
   b. niacin.
   c. isoniazid.
   d. ACE-inhibitors.

6. The most common adverse drug event of insulin therapy is:
   a. hypoglycemia.
   b. an allergic reaction.
   c. an injection-site reaction.
   d. pruritus.

7. Which of the following is true regarding administration of insulin lispro and aspart?
   a. They should be administered 45 minutes before a meal.
   b. They can be mixed with NPH or ultralente insulin.
   c. Both are FDA-approved for subcutaneous infusion through a pump in the abdomen.
   d. Compared with regular insulin, they result in a slower reduction in blood sugar after meals.

8. All of the following statements about insulin glargine are true except:
   a. It is associated with a similar rate of hypoglycemic events and glucose control compared with other insulins.
   b. It is appropriate for patients with continuous nocturnal hypoglycemia who are not meeting HbA1c goals with NPH insulin.
   c. It produces peaks and troughs during insulin coverage.
   d. It is recommended for patients who are just beginning intermediate or long-acting insulin therapy.

9. Newer insulin analogues present promising alternatives in which of the following situations?
   a. patients who are intolerant of regular or NPH insulin
   b. patients who have continued to experience hypoglycemic events
   c. patients who are not achieving tight glycemic control
   d. all of the above

10. Which of the following products are being investigated as newer therapies for insulin?
    a. inhaled insulin
    b. oral crystalline capsules
    c. dermal patch
    d. all of the above
CE Registration and Evaluation Form

Date of publication: February 2005
Title: An Evidence-Based Summary of Insulin Analogues
Authors: B. A. Fedutes, A. Calabrese Donihi, C. M. Culley, B. J. McCreery, N. T. Ansani
Submission deadline: February 28, 2006
ACPE Program # 079-999-05-014-H01

Registration

Name: ____________________________________________________________ Degree: ____________________________________
Street address: ______________________________________________  Last 4 Digits of Social Security No. (Web ID): __________
City: ___________________________________  State: _________  Zip:__________  Telephone: _____________________________
E-mail Address: _______________________________________   Check one:
   II  Physician
   II  Pharmacist
   II  Other

Time needed to complete this CE activity in hours:  □ 0.5 hr  □ 1 hr  □ 1.5 hr  □ 2 hr  □ Other _________________________

Certification: I attest to having completed this CE activity. ___________________________________________________________
   Signature (required) Date _______________

Answer Sheet

Please fill in the box next to the letter corresponding to the correct answer

1.   a   □  b   □  c   □  d   □
2.   a   □  b   □  c   □  d   □
3.   a   □  b   □  c   □  d   □
4.   a   □  b   □  c   □  d   □
5.   a   □  b   □  c   □  d   □
6.   a   □  b   □  c   □  d   □
7.   a   □  b   □  c   □  d   □
8.   a   □  b   □  c   □  d   □
9.   a   □  b   □  c   □  d   □
10.  a   □  b   □  c   □  d   □

Evaluation

Rate the extent to which:

<table>
<thead>
<tr>
<th>Very High</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
<th>Very Low</th>
</tr>
</thead>
</table>
1. Objectives of this activity were met
2. You were satisfied with the overall quality of this activity
3. Content was relevant to your practice needs
4. Participation in this activity changed your knowledge/attitudes
5. You will make a change in your practice as a result of participation in this activity
6. This activity presented scientifically rigorous, unbiased, and balanced information
7. Individual presentations were free of commercial bias
8. Adequate time was available for Q&A
9. Which ONE of the following best describes the impact of this activity on your performance:
   □ This program will not change my behavior because my current practice is consistent with what was taught.
   □ This activity will not change my behavior because I do not agree with the information presented.
   □ I need more information before I can change my practice behavior.
   □ I will immediately implement the information into my practice.
10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)
    □ Discuss new information with other professionals
    □ Consult the literature
    □ Discuss with industry representative(s)
    □ Participate in another educational activity
    □ Other _________________________

Send the completed form and $10 payment (make checks payable to P&T) to: Department of Health Policy, Jefferson Medical College, Attn: Continuing Education Credit, 1015 Walnut Street, Suite 115, Philadelphia, PA 19107.