

## REVIEW ARTICLE

## DRUG THERAPY

## Insulin Analogues

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THE DISCOVERY OF INSULIN MORE THAN 80 YEARS AGO IS CONSIDERED one of the greatest medical breakthroughs of the 20th century.<sup>1</sup> The first commercial insulin preparations contained numerous impurities and varied in potency from lot to lot by as much as 25 percent. Manufacturing techniques improved rapidly, however, which allowed the production of higher-quality formulations from bovine and porcine sources. In the 1930s, the first long-acting preparation, protamine zinc insulin, was developed to reduce the number of injections necessary for adequate insulin replacement.<sup>2</sup> This preparation was often used once daily, without the addition of regular insulin, which set a trend that lasted through the 1950s, when neutral protamine Hagedorn (NPH) and insulin zinc (Lente) were introduced. In the ensuing two decades, a movement toward more complete coverage of insulin requirements resulted in the twice-daily “split-mix” regimen of NPH and regular insulin that is used to this day.<sup>3</sup>

By the early 1980s, the development of purified pork insulin and then recombinant human insulin virtually eliminated insulin allergy and immune-mediated lipoatrophy. These achievements marked a slowdown in the innovation of insulin products until the 1990s, when the reports of the Diabetes Control and Complications Trial<sup>4</sup> and the United Kingdom Prospective Diabetes Study<sup>5</sup> confirmed the value of glycemic control in the delay or prevention of complications of diabetes. The limiting pharmacokinetic and pharmacodynamic features of standard insulins, which frequently lead to hypoglycemia as glycosylated hemoglobin values approach the normal range, renewed interest in producing safer insulin formulations that more closely duplicate the basal and meal-time components of endogenous insulin secretion. This interest has yielded insulin analogues that are characterized by action profiles that afford more flexible treatment regimens with a lower risk of the development of hypoglycemia (Tables 1 and 2). This article examines the use of these newer insulins in clinical practice.

Although the definitions are arbitrary, from a clinical viewpoint, insulin replacement consists of prandial (bolus) insulin, basal insulin, and a correction-dose insulin supplement.<sup>6</sup> Prandial insulin is given in an attempt to mimic the response of endogenous insulin to food intake. Normally, this response occurs in a robust first-phase secretion and then a more prolonged second-phase release into the portal circulation.<sup>7</sup> A subcutaneous injection of insulin will never precisely replicate the second-phase release. The basal-insulin component mimics the relatively small but constant release of insulin that regulates lipolysis and the output of hepatic glucose. Finally, correction-dose insulin addresses premeal or between-meal hyperglycemia, independently of the prandial insulin. According to these definitions, regular and NPH insulin span both the prandial and basal components of insulin replacement, whereas insulin analogues target each of these components separately.

## RAPIDLY ACTING ANALOGUES

The relatively slow absorption of regular insulin is attributed to the fact that when zinc atoms are added to the solution of dimers that make up regular insulin, the molecules

associate, and hexamers are formed. These larger molecules diffuse slowly into the circulation, whereas the insulin dimers and monomers are absorbed more quickly. Insulin lispro, the first rapidly acting analogue that was developed, differs from regular insulin by virtue of its capacity to dissociate rapidly into monomers in subcutaneous tissue. It was formulated on the premise that insulin-like growth factor 1 (IGF-1), which is structurally similar to insulin, does not tend to self-associate (Fig. 1), probably because of differences between the C-terminal portion of the B chain of IGF-1 and that of insulin. Inversion of the lysine of B29 and the proline of B28 of human insulin confers a conformational change that results in a shift in the normal binding of the C-terminal portion of the B chain, which in turn reduces the formation of dimers and hexamers.

The immunogenic profile of insulin lispro is similar to that of recombinant insulin.<sup>8</sup> Even before exposure to insulin lispro, there is an increase in cross-reactive antibodies (i.e., serum reacts with both insulin lispro and human insulin) but not in insulin-specific or lispro-specific antibody levels.<sup>8</sup> These antibodies decrease over time and have no clinical consequences.<sup>8,9</sup>

The second rapidly acting analogue that was introduced was insulin aspart<sup>10</sup> (Fig. 1). With its proline having been replaced by the negatively charged aspartic acid, this analogue has an insulin-receptor affinity similar to that of human insulin.

**PHARMACOKINETIC AND PHARMACODYNAMIC ISSUES**

The rapidly acting analogues lispro and aspart have similar pharmacokinetic (Fig. 2) and pharmacodynamic properties.<sup>11,12</sup> In general, injection of these rapidly acting analogues results in twice the maximal concentration and takes about half the time to reach the maximal concentration as do equivalent doses of regular insulin.

Clinically, the pharmacodynamic measure of the action of insulin is more indicative of its effect on blood glucose than is the pharmacokinetic measure. During a study involving the use of a euglycemic clamp, insulin was injected and then glucose infused to maintain steady glucose levels.<sup>11</sup> The maximal glucose-infusion rate is a measurement of the greatest activity of the insulin. Peak insulin action occurs approximately twice as fast with the analogues as with regular insulin. In one study, with a dose of 10 units of insulin lispro, the mean (±SD) peak insulin action was 99±39 minutes, as compared with 179±93 minutes for regular insulin

**Table 1. Duration of Action of Standard Insulins and Insulin Analogues.\***

Insulin	Onset of Action	Peak Action	Effective Duration
Standard			
Regular	30–60 min	2–3 hr	8–10 hr
NPH	2–4 hr	4–10 hr	12–18 hr
Zinc insulin (Lente)	2–4 hr	4–12 hr	12–20 hr
Extended zinc insulin (Ultralente)	6–10 hr	10–16 hr	18–24 hr
Analogues			
Lispro	5–15 min	30–90 min	4–6 hr
Aspart	5–15 min	30–90 min	4–6 hr
Glargine	2–4 hr	None	20–24 hr

\* Serum insulin profiles are based on a subcutaneous injection of 0.1 to 0.2 unit per kilogram of body weight; large variation within and between persons may be noted. Data are from DeWitt and Hirsch.<sup>6</sup>

**Table 2. Prices of Insulin Analogues.\***

Insulin Type	Price (\$)
Lispro, vial	58.99
Aspart, vial	68.38
Lispro mix (Humalog), 75/25, vial	64.62
Glargine, vial	57.76
Lispro, 3 ml, disposable pen†	85.01
Aspart, 3 ml, disposable pen†	83.52
Aspart mix (Novolog), † 70/30, disposable pen	89.39

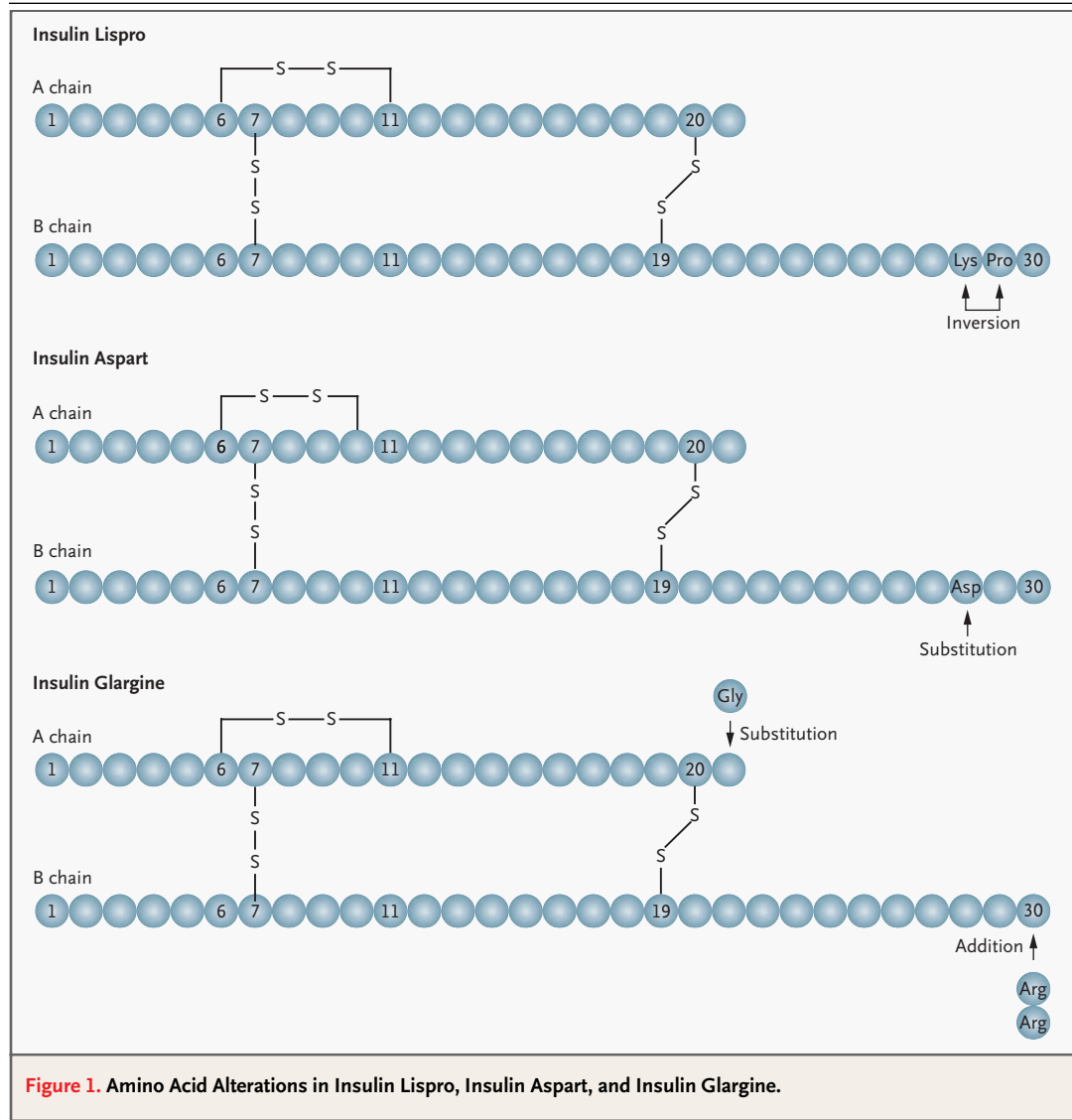
\* Prices are from www.drugstore.com (accessed December 1, 2004). All concentrations are 100 U per milliliter.  
† Price is normalized to 10 ml of insulin, but this product can be purchased only as five 3-ml pens.

( $P < 0.05$ ).<sup>11</sup> In a study of insulin aspart in which a dose of 0.2 unit per kilogram of body weight was used, the time to peak insulin action was 94±46 minutes for insulin aspart, as compared with 173±62 minutes for regular insulin ( $P < 0.001$ ).<sup>12</sup> Use of these rapidly acting analogues also results in less variability in absorption at the injection site and possibly in less variation between and within patients.<sup>11</sup>

**CLINICAL EFFECTIVENESS**

*Type 1 Diabetes*

Except in the case of insulin-pump therapy, the two rapidly acting analogues are used only as prandial insulin replacement. Both insulin lispro and insulin aspart are superior to regular insulin in the re-



**Figure 1.** Amino Acid Alterations in Insulin Lispro, Insulin Aspart, and Insulin Glargine.

duction of postprandial hyperglycemia.<sup>13,14</sup> However, in general, studies involving multiple daily injections have not demonstrated that rapidly acting analogues improve glycosylated hemoglobin levels.<sup>15-18</sup> This might be because the majority of these studies did not achieve ideal basal-insulin replacement or because the overall glycemic control was adequate at baseline, which makes significant improvements in average overall glycemia difficult to demonstrate. Nevertheless, it appears that an improvement in the control of postprandial hyperglycemia and the related glycemic variability,<sup>19</sup> which is not well captured by glycosylated hemoglobin, may be important in forestalling the development of diabetes-related complications. It is conceivable

that in their reduction of postprandial hyperglycemia, rapidly acting analogues (particularly in combination with long-acting analogues or continuous subcutaneous infusion of insulin) could have a greater effect than regular insulin on the reduction of complications of diabetes.

In one study, when basal-insulin replacement was maximized with small doses of mealtime and bedtime NPH insulin, insulin lispro improved glycosylated hemoglobin levels in comparison with regular insulin.<sup>20</sup> In general, studies have shown that rapidly acting analogues are superior to regular insulin for lowering glycosylated hemoglobin levels in patients who receive insulin by continuous subcutaneous infusion.<sup>21-23</sup>

### Type 2 Diabetes

For patients with type 2 diabetes in whom glyburide is not effective, the initiation of insulin therapy with insulin lispro taken at mealtimes was shown in one study to be more effective in improving glycosylated hemoglobin levels than was NPH insulin or metformin taken at bedtime.<sup>24</sup> The authors concluded that the addition of any second agent with a different mechanism of action would improve glycemic control but that the focus on postprandial hyperglycemia would optimize glycemic control. Insulin replacement with prandial insulin alone is rarely recommended but could be considered an option when insulin therapy is started in patients with type 2 diabetes.

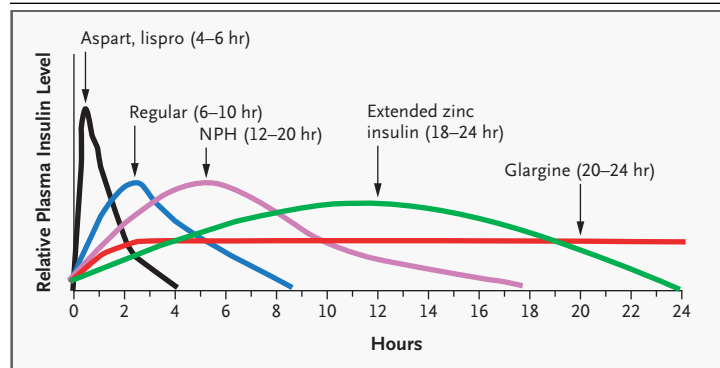
### HYPOGLYCEMIA

The more rapid pharmacodynamic effects of insulin lispro and insulin aspart make postabsorptive hypoglycemia less of a problem with these analogues than with regular insulin.<sup>13-15,20,25</sup> A large meta-analysis that represented more than 1400 patient-years reported a 25 percent reduction in the frequency of severe hypoglycemia (i.e., that which required the assistance of another person to correct) with the use of insulin lispro, as compared with regular insulin.<sup>26</sup> It is not surprising that hypoglycemia occurs earlier with a rapidly acting analogue than with regular insulin.<sup>20,25</sup> The faster action of the rapidly acting analogues also alters the timing in terms of the risk of exercise-induced hypoglycemia. Patients who exercise early in the postprandial period (one to three hours after a meal) require a decrease in the insulin dose, whereas those who exercise later (three to five hours) require a smaller change or none.<sup>27</sup>

### PRACTICAL ISSUES

Insulin pens have made prandial insulin replacement more practical. Another important consideration in regard to rapidly acting analogues is that less snacking is required with their use. When regular insulin is given at dinnertime, its action, which has a long duration, overlaps with that of nocturnal basal insulin and necessitates a bedtime snack. With rapidly acting analogues, such snacking is optional. Additional caloric intake at bedtime, unless intended for the treatment of hypoglycemia, will require additional prandial insulin.

The amount of time that elapses between the injection and a meal, also known as the lag time,<sup>6</sup> is critical in the control of postprandial hyperglycemia.



**Figure 2. Approximate Pharmacokinetic Profiles of Human Insulin and Insulin Analogues.**

The relative duration of action of the various forms of insulin is shown. The duration will vary widely both between and within persons.

For example, with initial glucose levels approximating 180 mg per deciliter (10 mmol per liter), postprandial hyperglycemia is minimized when the lag time is at least 15 minutes.<sup>28</sup> Longer lag times are more desirable when there is more profound premeal hyperglycemia.

### PREMIXED INSULINS

Two premixed insulins that contain rapidly acting analogues are available in the United States: neutral protamine lispro (insulin lispro protamine) and protamine crystalline aspart. (Basal insulin and prandial insulin are sold already mixed in a fixed ratio.) The former can be obtained in a 25 percent mixture of insulin lispro, whereas the latter is available in a 30 percent mixture of insulin aspart. Functionally, the protamine component of these two preparations is identical to that of NPH.<sup>6</sup> Studies have shown that, as compared with a premix of 70 percent NPH and 30 percent regular insulin, the premixed analogues result in reduced postprandial hyperglycemia but no changes in glycosylated hemoglobin levels.<sup>29,30</sup> It is difficult to recommend these preparations, which provide little flexibility, particularly for patients with severe insulin deficiency (i.e., most patients with type 1 diabetes and many with type 2), since there is not enough exogenous insulin available for lunchtime needs. Furthermore, when any premixed insulin is injected with a pen device, supplemental insulin for premeal hyperglycemia requires the separate injection of a rapidly acting analogue, since protamine insulin should not be used to correct a blood-glucose level that is higher than targeted. Therefore, premixed insulin

analogues should fill a relatively small niche for most patients who require prandial insulin, with two exceptions: those with type 2 diabetes who eat relatively small lunches and those who are unable to use more sophisticated regimens.

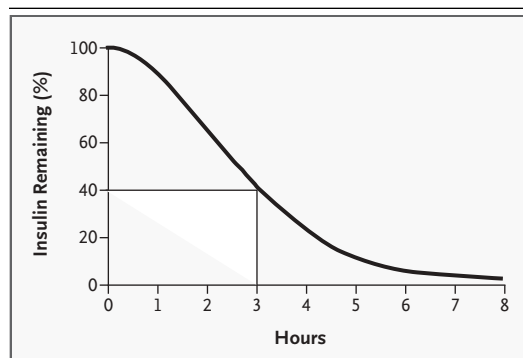
#### SELF-MONITORING OF BLOOD GLUCOSE

The most recent clinical-practice guidelines from the American Diabetes Association suggest that persons with type 1 diabetes should perform self-monitoring of blood glucose three or more times daily.<sup>31</sup> At the Diabetes Care Center of the University of Washington Medical Center, patients with type 1 diabetes who receive either multiple injections or insulin-pump therapy measure their blood sugar, on average, five times daily,<sup>32</sup> which suggests that many are measuring postprandial glucose levels. People who perform frequent blood-glucose testing must be cautious about “insulin stacking,” which refers to the practice of providing correction-dose insulin before a prior dose of prandial insulin (or the peak action of NPH insulin) has had its full effect.<sup>6</sup> For those patients who supplement additional insulin for premeal or between-meal hyperglycemia, knowledge about how much of the previous insulin has yet to be absorbed is important, since, otherwise, hypoglycemia may occur as a result of insulin stacking.

The effects of insulin stacking can best be appreciated by reviewing a study by Mudaliar and colleagues that involved the use of euglycemic clamping.<sup>12</sup> These investigators found that when 0.2 unit per kilogram of insulin aspart or regular insulin was injected subcutaneously into the abdomen in 20 nondiabetic subjects, the glucose infusion rates — a measure of insulin action — were prolonged in comparison with the insulin appearance rates. Regular insulin has its greatest action on blood glucose at 180 to 300 minutes, as opposed to 90 to 160 minutes for insulin aspart. Insulin aspart still has significant activity at 300 minutes (Fig. 3). There are also differences among patients in terms of absorption. The current models of insulin pumps have these data programmed into them so that insulin stacking is less of a danger.

#### LONG-ACTING ANALOGUES

The first of the long-acting insulin analogues, insulin glargine, was introduced in the United States in the spring of 2001. This analogue is produced by the substitution of glycine for asparagine at posi-



**Figure 3. The Timing of Action for Insulin Aspart.**

A euglycemic clamp is used for delivery of the insulin aspart (0.2 U per kilogram of body weight, delivered into the abdomen). The use of this graph helps patients avoid “insulin stacking.” For example, three hours after the administration of 10 units of insulin aspart, one can estimate that there is still 40 percent times 10 units, or 4 units, of insulin remaining. Adapted from Mudaliar et al.<sup>12</sup>

tion A21 of the insulin molecule and by the addition of two arginine molecules at position B30 (Fig. 1). These changes lead to a shift in the isoelectric point toward a neutral pH, which results in an insulin molecule that is less soluble at the injection site and that precipitates in the subcutaneous tissue to form a depot from which insulin is slowly released<sup>33</sup> (Fig. 2).

#### PHARMACOKINETIC AND PHARMACODYNAMIC ISSUES

As compared with NPH insulin, insulin glargine results in prolonged insulin absorption and shows little peak activity, as demonstrated by differences in disappearance curves.<sup>34</sup> Rates of absorption of insulin glargine at various sites do not differ.<sup>34</sup> Furthermore, there is no evidence that insulin glargine accumulates after multiple injections.<sup>35</sup> Pharmacodynamic data are consistent with these observations, since metabolic activity in normal volunteers lasts for up to 30 hours.<sup>36</sup> By way of comparison, NPH insulin reaches a peak between 4 and 8 hours and then falls off rapidly, with a duration of 12 to 14 hours.<sup>36</sup> In another pharmacodynamic study, insulin glargine was found to have no peak and to have a mean ( $\pm$ SE) duration of action of  $22\pm 4$  hours.<sup>37</sup> Variation among subjects in the rates of glucose infusion required to maintain euglycemia after injection is also lower with glargine than with both NPH and extended zinc insulin (Ultralente).<sup>37</sup>

It is important not to overinterpret the pharmacodynamic studies, because the data presented are simply averages of the results obtained in a relatively small number of subjects. The onset or duration of action may be substantially longer or shorter in individual patients. Furthermore, doses of insulin that are different from those in the studies cited here or use in different patient populations (e.g., children) may result in different profiles of action.

#### CLINICAL EFFECTIVENESS

##### *Type 1 Diabetes*

Most studies involving insulin glargine have compared it with NPH insulin. Because insulin glargine is clear and NPH is a cloudy suspension, clinical trials have been open label. In general, the trials have shown no differences or occasional improvements in glycemic control with insulin glargine, although a reduction in the risk of hypoglycemia, especially nocturnal hypoglycemia, has been the rule with insulin glargine. When insulin glargine was given to patients with type 1 diabetes at either dinnertime or bedtime, the glycosylated hemoglobin level decreased from baseline, whereas no change in glycosylated hemoglobin was noted among those who received four injections of NPH as the basal insulin replacement.<sup>38</sup> As compared with the subjects who received NPH insulin, those receiving insulin glargine were less likely to have hypoglycemia at dinnertime or bedtime, despite final glycosylated hemoglobin levels of 6.4 percent and 6.6 percent, respectively (normal value, less than 6.5 percent).<sup>38</sup> However, in two U.S. studies involving subjects with type 1 diabetes, one in which prandial regular insulin was used for 28 weeks in 534 subjects<sup>39</sup> and the other in which prandial insulin lispro was used for 16 weeks in 619 subjects,<sup>40</sup> glycosylated hemoglobin levels did not differ according to whether the basal insulin was insulin glargine or NPH insulin. In these two studies, the risk of hypoglycemia was reduced (by 39.9 percent and 49.2 percent, respectively) only when regular insulin was used as the prandial insulin.<sup>39</sup>

##### *Type 2 Diabetes*

For persons with type 2 diabetes, insulin glargine appears to be as effective as NPH insulin when insulin is added to oral hypoglycemic agents. In the largest trial reported to date, Riddle et al. evaluated 756 subjects with type 2 diabetes and a mean glycosylated hemoglobin level of 8.6 percent who were randomly assigned to receive insulin glargine or

NPH insulin without any prandial insulin injections.<sup>41</sup> Although glycosylated hemoglobin levels below 7 percent were achieved in approximately 60 percent of the subjects in both groups, there was a greater frequency of nocturnal hypoglycemia in the group receiving the NPH insulin.

For patients with type 2 diabetes and higher initial levels of blood glucose than those noted in the study by Riddle et al.<sup>41</sup> (e.g., glycosylated hemoglobin levels above 10 percent), it becomes even more difficult to reach a target value for glycosylated hemoglobin of 7 percent with basal insulin alone. In one study of 426 subjects whose initial glycosylated hemoglobin levels were close to 9 percent and who were assigned to receive either insulin glargine or NPH insulin, the glycosylated hemoglobin levels were still above 8 percent at 12 months, irrespective of the study group.<sup>42</sup> For those in whom a target fasting blood-glucose level of 121 mg per deciliter (6.7 mmol per liter) was reached with insulin glargine or NPH insulin, glycosylated hemoglobin levels were still high — 7.7 and 7.6 percent, respectively, at the end of the 12-month study. One possible reason that the diabetes was not better controlled is that, on average, only about 20 units of insulin was used for the subjects in each group. Still, symptomatic hypoglycemia was noted in 33 percent of the subjects who received insulin glargine, as compared with 41 percent of those who received NPH insulin ( $P=0.04$ ).<sup>42</sup> As in the study by Riddle et al.,<sup>41</sup> nocturnal hypoglycemia was reported less frequently with insulin glargine than with NPH insulin ( $P<0.001$ ).<sup>42</sup> Similar reductions in the frequency of nocturnal hypoglycemia were reported in another study that compared insulin glargine with NPH insulin, with no difference in glycosylated hemoglobin levels between the groups.<sup>43</sup>

Several questions concerning optimal therapy emerge from these studies. First, when is it most appropriate to use a combination of basal insulin and prandial insulin in patients with type 2 diabetes? Despite evidence that, for many of these patients, basal insulin alone will reduce the level of glycosylated hemoglobin to less than 7 percent, baseline glycosylated hemoglobin levels in patients in the majority of studies, including those noted above, were only moderately above the target at the beginning of the protocol. For example, in the studies discussed above, baseline glycosylated hemoglobin levels were approximately 8.6 percent,<sup>41</sup> 9.0 percent,<sup>42</sup> and 8.5 percent.<sup>43</sup> In the United States, insulin therapy is often started only when



much higher glucose levels than these are present. In one cohort study involving 1738 patients in a primary care practice, when insulin therapy was initiated, the mean glycosylated hemoglobin level was 10.4 percent.<sup>44</sup> Given this common clinical scenario, in many patients, glycemic targets will not be achieved with basal insulin alone.

The next question pertains to the timing of the injections of basal insulin. A bedtime NPH injection as basal insulin has generally appeared to be superior to a morning injection of the same dose.<sup>45,46</sup> Most large studies of type 2 diabetes that evaluated insulin glargine without prandial insulin were performed with the use of bedtime injections. However, one large study involving 695 subjects with type 2 diabetes reported greater reductions in glycosylated hemoglobin levels with morning injections of insulin glargine than with bedtime injections (both groups also received glimepiride in the morning).<sup>47</sup> Similarly, in 378 subjects with type 1 diabetes who received once-daily insulin glargine and prandial insulin lispro, the 24-hour glucose profiles were identical, regardless of whether the basal insulin was injected at breakfast, dinner, or bedtime.<sup>48</sup> However, emerging data suggest that the provision of a once-daily dose of insulin glargine as the basal insulin may not be effective for all patients with severe insulin deficiency, particularly those with type 1 diabetes.<sup>49</sup>

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#### SPECIAL POPULATIONS

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##### CHILDREN

The use of insulin in children will continue to increase as the incidence of diabetes in this population grows.<sup>50</sup> One practical issue pertains to the use of rapidly acting analogues in school-age children, who often want snacks late in the afternoon. One option is to inject a small additional prandial dose of either insulin aspart or insulin lispro, but some diabetologists prefer to prescribe regular insulin before lunch, which results in late-afternoon hyperinsulinemia and necessitates a snack.

As compared with the findings for adults, there are far fewer data concerning the use of insulin glargine in children. No pharmacokinetic studies have been conducted in children, although there has been one report of lower nocturnal free insulin levels in children who received insulin glargine than in those who received NPH insulin.<sup>51</sup> One study of 349 children who were 5 to 16 years old showed no difference in glycosylated hemoglobin levels be-

tween children who received insulin glargine and those who received NPH insulin, although less severe hypoglycemia was observed in the group that received insulin glargine.<sup>52</sup> Similar data were reported in a study involving 114 children who were given insulin glargine at bedtime and NPH insulin in the morning so that lunchtime prandial insulin would not be required.<sup>53</sup>

##### PREGNANT WOMEN

Data from prospective, blinded, randomized clinical trials of insulin analogues in pregnancy are lacking. However, retrospective analysis has not shown any significant difference between insulin lispro and regular insulin in regard to either fetal or maternal outcomes. Indeed, the largest amount of data regarding safety in pregnancy for any insulin analogue is for insulin lispro. One report noted that there was no transplacental passage of insulin lispro at blood levels similar to those generally evaluated with other forms of exogenous insulin therapy.<sup>54</sup>

For example, Bhattacharyya and colleagues reported that there were no differences in gestational outcomes between a group given regular insulin (138 subjects) and a group given insulin lispro (75 subjects), although glycosylated hemoglobin levels were lower with the analogue.<sup>55</sup> Other recent reports have reached similar conclusions.<sup>56,57</sup>

The greatest concern about the administration of insulin lispro in pregnancy resulted from a 1999 report that in 3 of 10 women who received this agent during pregnancy, diabetic retinopathy developed by the third trimester.<sup>58</sup> However, a more recent prospective, open-label study involving 69 pregnant women with type 1 diabetes revealed no differences in the frequency of diabetic retinopathy between women who received insulin lispro and those who received regular insulin during pregnancy, and glycosylated hemoglobin levels were significantly lower with the analogue after the first trimester.<sup>59</sup> Most experts now agree that insulin lispro can be used safely in pregnancy.<sup>60</sup>

Similar data on outcomes are not available for either insulin aspart or insulin glargine. However, studies of IGF-1-receptor binding and the metabolic and mitogenic potencies of insulin glargine indicated that there was an increase in both IGF-1-receptor affinity and mitogenic potency in a cell-culture model that used human osteosarcoma cells.<sup>61</sup> There are theoretical toxicologic effects of these changes. For example, IGF-1 has been implicated in the development of mammary, ovarian,

and bone tumors in addition to the development of diabetic retinopathy. As a result, many consider it unwise to use insulin glargine in pregnancy.

insulin lispro and insulin aspart. In the future, both inhaled insulin<sup>66</sup> and oral insulin<sup>67</sup> may have a role in prandial insulin replacement.

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#### CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

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Both insulin lispro and insulin aspart are approved for administration as a continuous subcutaneous insulin infusion. A recent meta-analysis that compared insulin analogues with regular human insulin included six studies — one parallel, randomized, controlled trial and five randomized, crossover studies.<sup>62</sup> The authors concluded that there was a small but significant reduction in glycosylated hemoglobin levels, 0.26 percent (95 percent confidence interval, 0.06 to 0.47 percent;  $P=0.01$ ), with the rapidly acting analogues.<sup>62</sup> Several of the studies that were included in the meta-analysis showed that there was a lower frequency of hypoglycemia with the analogues, but this result varied according to the definition used.

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#### NEW ANALOGUES

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Two insulin analogues will be introduced in the near future. Insulin detemir, a long-acting analogue of neutral pH, is an acylated derivative of human insulin.<sup>63</sup> After injection, insulin detemir binds to albumin through a fatty-acid chain attached to the lysine at residue B29, which leads to a reduction in free detemir levels. The initial data suggest that this compound has less variability in absorption than does NPH, a feature associated with a reduced risk of hypoglycemia and also weight loss.<sup>64</sup> As compared with insulin glargine, insulin detemir appears to have a shorter time-action profile, which necessitates twice-daily injections in persons with type 1 diabetes.<sup>65</sup>

Insulin glulisine is a rapidly acting analogue with a pharmacokinetic profile that is similar to those of

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#### CONCLUSIONS

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The evolution in insulins — from those produced from animal species to human-insulin preparations produced with recombinant DNA technology to the present-day insulin analogues — represents more than 80 years of collaboration among protein chemists, clinical researchers, and millions of people with diabetes. Insulin treatment has always been as much an art as a science.<sup>3</sup> The introduction of better tools for the monitoring of glycemic control, coupled with evidence that near-normal glycosylated hemoglobin levels reduce the risk of diabetic complications, has increased the demand for insulin preparations that have greater effectiveness, safety, and versatility. Insulin analogues have met this demand, in large part, by the allowance of discrete, and therefore more accurate, replication of the basal and prandial components of insulin replacement, with an attendant decrease in the risk of hypoglycemia. The proper use of insulin analogues allows people with diabetes greater flexibility in the timing of meals, snacks, and exercise, which in turn enhances their ability to lead normal lives. Nevertheless, current insulin-replacement regimens are far from perfect; to date, it is impossible to replicate normal insulin secretion. Furthermore, for some people, especially children and adolescents, a regimen of injecting insulin four times or more each day may be so challenging that at least occasional failure is inevitable. I therefore look forward to new forms of technology that will help improve insulin-replacement therapy.

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Dr. Hirsch reports having received consulting and lecture fees from Aventis, Novo Nordisk, Eli Lilly, and Medtronic MiniMed.

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#### REFERENCES

- Rosenfeld L. Insulin: discovery and controversy. *Clin Chem* 2002;48:2270-88.
- Joslin EP. A diabetic manual for the mutual use of doctor and patient. 7th ed. Philadelphia: Lea & Febiger, 1941.
- Jackson RL. Historical background. In: Jackson RL, Guthrie RA. The physiological management of diabetes in children. New York: Medical Examination Publishing, 1986: 6-16.
- Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53. [Erratum, *Lancet* 1999;354:602.]
- DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA* 2003;289: 2254-64.
- Ward WK, Bolgiano DC, McKnight B, Halter JB, Porte D Jr. Diminished B-cell secretory capacity in patients with noninsu-



- lin-dependent diabetes mellitus. *J Clin Invest* 1984;74:1318-28.
8. Fineberg NS, Fineberg SE, Anderson JH, Birkett MA, Gibson RG, Hufford S. Immunologic effects of insulin lispro [Lys (B28), Pro (B29) human insulin] in IDDM and NIDDM patients previously treated with insulin. *Diabetes* 1996;45:1750-4.
  9. Fineberg SE, Huang J, Brunelle R, Gulliya KS, Anderson JH Jr. Effect of long-term exposure to insulin lispro on the induction of antibody response in patients with type 1 or type 2 diabetes. *Diabetes Care* 2003;26:89-96.
  10. Simpson KL, Spencer CM. Insulin aspart. *Drugs* 1999;57:759-65.
  11. Howey DC, Bowshe RR, Brunelle RL, Woodworth JR. [Lys(B28), Pro(B29)]-human insulin: a rapidly absorbed analogue of human insulin. *Diabetes* 1994;43:396-402.
  12. Mudaliar S, Lindberg FA, Joyce M, et al. Insulin aspart (B28 Asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. *Diabetes Care* 1999;22:1501-6.
  13. Anderson JH Jr, Brunelle RL, Koivisto VA, et al. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. *Diabetes* 1997;46:265-70.
  14. Home PD, Lindholm A, Hylleberg B, Round P. Improved glycemic control with insulin aspart: a multicenter randomized double-blind crossover trial in type 1 diabetic patients. *Diabetes Care* 1998;21:1904-9.
  15. Pflutzner A, Kustner E, Forst T, et al. Intensive insulin therapy with insulin lispro in patients with type 1 diabetes reduces the frequency of hypoglycemic episodes. *Exp Clin Endocrinol Diabetes* 1996;104:25-30.
  16. Vignati L, Anderson JH Jr, Iversen PW. Efficacy of insulin lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin-dependent diabetes mellitus. *Clin Ther* 1997;19:1408-21.
  17. Colombel A, Murat A, Krempf M, Kuchly-Anton B, Charbonnel B. Improvement of blood glucose control in Type 1 diabetic patients treated with lispro and multiple NPH injections. *Diabet Med* 1999;16:319-24.
  18. Gale EA. A randomized, controlled trial comparing insulin lispro with human soluble insulin in patients with Type 1 diabetes on intensified insulin therapy. *Diabet Med* 2000;17:209-14.
  19. Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. *Diabetes* 2003;52:2795-804.
  20. Lalli C, Ciofetta M, Del Sindaco P, et al. Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. *Diabetes Care* 1999;22:468-77.
  21. Zinman B, Tildesley H, Chiasson JL, Tsui E, Strack T. Insulin lispro in CSII: results of a double-blind crossover study. *Diabetes* 1997;46:440-3. [Erratum, *Diabetes* 1997;46:1239.]
  22. Renner R, Pflutzner A, Trautmann M, Harzer O, Sauter K, Landgraf R. Use of insulin lispro in continuous subcutaneous insulin infusion treatment: results of a multicenter trial. *Diabetes Care* 1999;22:784-8.
  23. Raskin P, Holcombe JH, Tamborlane WV, et al. A comparison of insulin lispro and buffered regular human insulin administered via continuous subcutaneous insulin infusion pump. *J Diabetes Complications* 2001;15:295-300.
  24. Bastyr EJ III, Stuart CA, Brodows RG, et al. Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA1c. *Diabetes Care* 2000;23:1236-41.
  25. Burge MR, Castillo KR, Schade DS. Meal composition is a determinant of lispro-induced hypoglycemia in IDDM. *Diabetes Care* 1997;20:152-5.
  26. Brunelle BL, Llewelyn J, Anderson JH Jr, Gale EA, Koivisto VA. Meta-analysis of the effect of insulin lispro on severe hypoglycemia in patients with type 1 diabetes. *Diabetes Care* 1998;21:1726-31.
  27. Tuominen JA, Karonen S-L, Melamies L, Bolli G, Koivisto VA. Exercise-induced hypoglycaemia in IDDM patients treated with a short-acting insulin analogue. *Diabetologia* 1995;38:106-11.
  28. Rassam AG, Zeise TM, Burge MR, Schade DS. Optimal administration of lispro insulin in hyperglycemic type 1 diabetes. *Diabetes Care* 1999;22:133-6.
  29. Koivisto VA, Tuominen JA, Ebeling P. Lispro Mix25 insulin as premeal therapy in type 2 diabetic patients. *Diabetes Care* 1999;22:459-62.
  30. Kilo C, Mezitis N, Jain R, Mersey J, McGill J, Raskin P. Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. *J Diabetes Complications* 2003;17:307-13.
  31. American Diabetes Association. Position Statement: standards of medical care in diabetes. *Diabetes Care* 2004;27:Suppl 1:S15-S35.
  32. Rudolph J, Hirsch IB. Assessment of therapy with continuous subcutaneous insulin infusion in an academic diabetes clinic. *Endocr Pract* 2002;8:401-5.
  33. Bolli GB, Di Marchi RD, Park GD, Pramming S, Koivisto VA. Insulin analogues and their potential in the management of diabetes mellitus. *Diabetologia* 1999;42:1151-67.
  34. Owens DR, Coates PA, Luzio SD, Tinbergen JP, Kurzhals R. Pharmacokinetics of 125I-labeled insulin glargine (HOE 901) in healthy men: comparison with NPH insulin and the influence of different subcutaneous injection sites. *Diabetes Care* 2000;23:813-9.
  35. Heise T, Bott S, Rave K, Dressler A, Roskamp R, Heinemann L. No evidence for accumulation of insulin glargine (Lantus): a multiple injection study in patients with Type 1 diabetes. *Diabet Med* 2002;19:490-5.
  36. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlack M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH and placebo. *Diabetes Care* 2000;23:644-9.
  37. Lepore M, Pampanelli S, Fanelli C, et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 2000;49:2142-8.
  38. Rossetti P, Pampanelli S, Fanelli C, et al. Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime. *Diabetes Care* 2003;26:1490-6.
  39. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. *Diabetes Care* 2000;23:639-43.
  40. Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. *Diabetes Care* 2000;23:1666-71.
  41. Riddle MC, Rosenstock J, Gerich J. The Treat-to-Target Trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;26:3080-6.
  42. Yki-Järvinen H, Dressler A, Ziemer M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care* 2000;23:1130-6.
  43. Rosenstock J, Schwartz SL, Clark CM Jr, Park GD, Donley DW, Edwards MB. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care* 2001;24:631-6.
  44. Haywood RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: effectiveness, complications, and resource utilization. *JAMA* 1997;278:1663-9. [Erratum, *JAMA* 1999;281:1989.]
  45. Seigler DE, Olsson GM, Skyler JS. Morning versus bedtime isophane insulin in type 2 (non-insulin dependent) diabetes mellitus. *Diabet Med* 1992;9:826-33.
  46. Yki-Järvinen H, Kauppila M, Kujansuu E, et al. Comparison of insulin regimens in

- patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1992;327:1426-33.
47. Fritsche A, Schweitzer MA, Haring HU. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* 2003;138:952-9.
48. Hamann A, Matthaer S, Rosak C, Silvestre L. A randomized clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with type 1 diabetes. *Diabetes Care* 2003;26:1738-44.
49. Albright ES, Desmond R, Bell DSH. Efficacy of conversion from bedtime NPH insulin injection to once- or twice-daily injections of insulin glargine in type 1 diabetic patients using basal/bolus therapy. *Diabetes Care* 2004;27:632-3.
50. Devendra D, Liu E, Eisenbarth GS. Type 1 diabetes: recent developments. *BMJ* 2004;328:750-4.
51. Mohn A, Strang S, Wernicke-Panten K, Lang AM, Edge JA, Dunger DB. Nocturnal glucose control and free insulin levels in children with type 1 diabetes by use of the long-acting insulin HOE 901 as part of a three-injection regimen. *Diabetes Care* 2000;23:557-9.
52. Schober E, Schoenle E, Van Dyk J, Wernicke-Panten K. Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2002;15:369-76.
53. Chase HP, Dixon B, Pearson J, et al. Reduced hypoglycemic episodes and improved glycemic control in children with type 1 diabetes using insulin glargine and neutral protamine Hagedorn insulin. *J Pediatr* 2003;143:737-40.
54. Boskovic R, Feig DS, Derewlany L, Knie B, Portnoi G, Koren G. Transfer of insulin lispro across the human placenta: in vitro perfusion studies. *Diabetes Care* 2003;26:1390-4.
55. Bhattacharyya A, Brown S, Hughes S, Vice PA. Insulin lispro and regular insulin in pregnancy. *QJM* 2001;94:255-60.
56. Masson EA, Patmore JE, Brash PD, et al. Pregnancy outcome in Type 1 diabetes mellitus treated with insulin lispro (Humalog). *Diabet Med* 2003;20:46-50.
57. Garg SK, Frias JP, Anil S, Gottlieb PA, MacKenzie T, Jackson WE. Insulin lispro therapy in pregnancies complicated by type 1 diabetes: glycemic control and maternal and fetal outcomes. *Endocr Pract* 2003;9:187-93.
58. Kitzmiller JL, Main E, Ward B, Theiss T, Peterson DL. Insulin lispro and the development of proliferative diabetic retinopathy during pregnancy. *Diabetes Care* 1999;22:874-6.
59. Loukovaara S, Immonen I, Teramo KA, Kaaja R. Progression of retinopathy during pregnancy in type 1 diabetic women treated with insulin lispro. *Diabetes Care* 2003;26:1193-8.
60. Gabbe SG, Graves CR. Management of diabetes mellitus complicating pregnancy. *Obstet Gynecol* 2003;102:857-68.
61. Kurtzhals P, Schäffer L, Sørensen A, et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. *Diabetes* 2000;49:999-1005.
62. Colquitt J, Royle P, Waugh N. Are analogue insulins better than soluble in continuous subcutaneous insulin infusion? Results of a meta-analysis. *Diabet Med* 2003;20:863-6.
63. Kurtzhals P, Havelund S, Jonassen I, et al. Albumin binding of insulins acylated with fatty acids: characterization of the ligand-protein interaction and correlation between binding affinity and timing of the insulin effect *in vivo*. *Biochem J* 1995;312:725-31.
64. Vague P, Selam J-L, Skeie S, et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. *Diabetes Care* 2003;26:590-6.
65. Bott S, Tusek C, Jacobsen LV, Kristensen A, Heise T. Insulin detemir reaches steady-state after the first day of treatment and shows a peakless time-action profile with twice-daily applications. In: International Diabetes Federation Abstract Volume of the 18th Congress, August 24-29, 2003, Paris, France. abstract.
66. Skyler JS, Cefalu WT, Kourides IA, et al. Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomised proof-of-concept study. *Lancet* 2001;357:331-5.
67. Clement S, Dandona P, Still JG, Kosutic G. Oral modified insulin (HIM2) in patients with type 1 diabetes mellitus: results from a phase I/II clinical trial. *Metabolism* 2004;53:54-8.

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