An Overview of Concentrated Insulin Products

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IN BRIEF This article provides a summary of the use of available concentrated insulins in the outpatient treatment of patients with diabetes. Concentrated insulins work through the same mechanisms as other insulin products. They vary from each other in concentrations and pharmacokinetic/pharmacodynamics profiles but are each similar to their U-100 concentration counterparts. Patient education is important to minimize errors and the risk of hypoglycemia when using these insulin formulations.

Type 2 diabetes is characterized by insulin resistance and relative insulin insufficiency. Epidemiological data suggest an association between patient weight and type 2 diabetes. Circulating levels of free fatty acids tend to be higher in patients with central obesity, worsening insulin resistance and increasing the demand for insulin production. Despite the availability of several agents with novel mechanisms of action to improve glycemic control, most patients with type 2 diabetes ultimately require the addition of insulin to their therapeutic regimen (1,2).

For many drugs, observed differences in response depend on how the molecule exerts its effect at the target receptor. All insulin products produce the same response at insulin receptors in the body. Differences in onset, peak, and duration of effect are entirely related to rates of molecule dissociation in the subcutaneous compartment. When regular insulin is injected under the skin, it forms hexamers, which break into dimers, and then monomers. Because insulin is a large protein, only the monomeric insulin molecules are small enough to be absorbed into the systemic circulation. The addition of protamine to regular insulin (to form neutral protamine Hagedorn, or NPH, insulin) adds an extra step in the dissociation of insulin molecules, increasing the duration of effect. The extended duration of insulin glargine results from changes in its amino acid sequence that require an acidic pH to remain in solution. Injection of the acidic solution under the skin results in formation of microprecipitates, which must first dissolve before the subsequent progression through hexamers, dimers, and monomers can take place.

As patients continue to gain weight and experience progressive β-cell failure over their lifespan, their demand for exogenous insulin increases. Increased doses of insulin in the subcutaneous compartment result in increased aggregation of hexamers and prolonged duration of effect.

The concentration of traditional insulin products is 100 units/mL (U-100). However, the growing number of patients who require very high insulin doses created a market for more concentrated insulin products. U-500 regular insulin was the first concentrated insulin to be marketed in the United States. As with U-100 insulin, higher doses of U-500

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insulin result in prolonged duration of action. For example, when the volume of U-500 insulin is >0.12 mL, or 60 units, the pharmacokinetics resemble those of NPH insulin, with a peak at 4 hours and duration of action >10 hours (3). The remainder of this article will review the characteristics of several newer concentrated insulins that are now available in addition to U-500.

Glargine U-300

Structure

Glargine U-300, sold under the trade name Toujeo, is a long-acting insulin for subcutaneous injection, containing 300 units/mL of insulin glargine. It is approved for use in patients with type 1 or type 2 diabetes. Glargine U-300 contains three times the amount of insulin per milliliter as glargine U-100. Glargine is a human insulin analog and differs from regular human insulin where the amino acid asparagine at position A21 is replaced by glycine, and two arginines remain at the C-terminus of the B-chain in glargine. Chemically, glargine and human insulin have identical empirical formulas and chemical weights. The pH of glargine is adjusted to 4, allowing it to become completely soluble. After injection into subcutaneous tissue, the acidic solution is neutralized, and glargine may precipitate out and slowly release itself into the systemic circulation (4).

Pharmacodynamics and Pharmacokinetics

Single doses of glargine U-300 (0.4, 0.6, and 0.9 units/kg) have been evaluated in patients with type 1 diabetes compared to glargine U-100 in a euglycemic clamp study. On a unit-to-unit basis, U-300 had a lower maximum and 24-hour glucose-lowering effect (4). In another study, the pharmacodynamics of U-300 was evaluated after 8 days of daily injection in 30 patients with type 1 diabetes. At steady state, the 24-hour glucose-lowering effect of U-300 (0.4 units/kg) was 27% lower and had a different distribution profile than that of an equivalent dose of U-100. This glucose-lowering effect increased with each daily administration (4).

The median times to maximum serum insulin concentration for glargine U-300 are 12, 12, and 16 hours for single 0.4, 0.6, and 0.9 unit/kg doses, respectively. Steady state is reached by at least 5 days of once-daily doses of 0.4–0.6 units/kg in people with type 1 diabetes. Glargine is metabolized at the carboxyl terminus of the B-chain with formation of two active metabolites (M1 and M2), with in vitro activity similar to that of human insulin. Glargine U-300 has not been evaluated in obese patients or in geriatric or pediatric populations.

Efficacy and Safety

In several open-label, multicenter trials, the efficacy and safety of glargine U-300 was compared to glargine U-100 in patients with type 2 diabetes who were already using basal insulin and oral hypoglycemic agents or rapid-acting insulin for mealtime injections. Dose adjustments were once per week based on the three previous self-monitoring of blood glucose (SMBG) results, with a target of 80–100 mg/dL. After 6 months, investigators evaluated change in A1C and the percentage of patients who experienced nocturnal or severe hypoglycemic events from week 9 to month 6 of treatment. Fasting blood glucose, SMBG results, mean insulin dose, weight change, and the number of patients experiencing ≥1 hypoglycemic events (as well as annual rates of hypoglycemic events) were also evaluated.

In the EDITION 2 trial, glycemic control improved similarly in both groups, but a 10% higher dose of U-300 was necessary. Reduction in A1C was also comparable, with similar proportions of patients reaching a target A1C of <7.0% and target fasting glucose levels <120 mg/dL. Mean prebreakfast (fasting) SMBG was lower with U-100 than with U-300 in the first 8 weeks; a more gradual decrease was seen with U-300 (5).

In the EDITION 1 trial, reduction of post-dinner and bedtime glucose levels was greater with U-300. Daily basal insulin doses were steadily increased to the same extent in both groups. Weight gain was noted in both groups, with more weight gain for U-100 noted in the EDITION 1 trial (5,6). There was less nocturnal or severe hypoglycemia in the U-300 group throughout the study period, presumably because of the extended release of glargine from subcutaneous depots resulting in a smoother, more stable, and prolonged pharmacokinetic/pharmacodynamic profile. The most common adverse drug reactions for both groups were similar and included infection, central nervous system disorders, gastrointestinal events, and musculoskeletal complaints. Overall, glargine U-300 resulted in a 23% reduction in risk of at least one nocturnal hypoglycemic event from week 9 to the end of treatment compared to glargine U-100. Annual rates of hypoglycemia were similar for both groups. More injection site reactions were noted with the U-300 formulation.

Delivery and Handling

Glargine U-300 is available as an injection containing 300 units/mL of insulin glargine. There is a maximum of 80 units/injection. It is a clear, colorless solution in 1.5-mL disposable prefilled pens (450 units/1.5 mL) that are sold in packages of three or five pens. The pens require the use of pen needles, which are sold separately (4).

Prefilled U-300 pens should not be stored in the freezer or allowed to freeze and should be discarded if frozen. If unopened, these pens should be stored in a refrigerator (36–46°F) and discarded after the expiration date. If opened and in use, the pens should not be refrigerated, but rather kept at room temperature (<86°F) away from direct light and heat. They must be discarded 28 days after being opened. The pen solution should not

be mixed or diluted with any other insulin or solutions (4).

Bottom Line

For 12 months, glycemic control was better sustained, and fewer patients reported hypoglycemia with glargine U-300 than with glargine U-100, although U-300 required a 14% higher dose to be comparably effective to U-100 (5,6).

Insulin Lispro U-200

Structure

Insulin lispro U-200, sold under the trade name Humalog U-200, is a commonly used rapid-acting insulin analog. It differs from human insulin in its amino acid profile, where a proline at position B28 is replaced by lysine, and a lysine at position B29 is replaced by proline. Empirically, both its chemical formula and molecular weight are identical to that of human insulin. As a sterile, aqueous, clear, and colorless solution, each milliliter of lispro U-200 contains 200 units of insulin lispro, compared with insulin lispro U-100, which contains 100 units/mL of insulin lispro (approximately half the concentration of the U-200 formulation). Lispro U-200 also has a pH of 7.0–7.8 (7).

Pharmacodynamics and Pharmacokinetics

Lispro is equipotent to human insulin; 1 unit of lispro has the same glucose-lowering effect as 1 unit of regular human insulin. However, lispro has a more rapid onset of action and a shorter duration of activity compared to regular human insulin when administered subcutaneously.

The pharmacodynamics of a single 20-unit dose of lispro U-200 have been studied compared to a single dose of lispro U-100 in a euglycemic clamp study with healthy subjects. The study concluded that the overall, maximum, and time to maximum glucose-lowering effects were similar between U-200 and U-100. This was also true for the mean area under the glucose infusion rate curves, a measure of the overall pharmacodynamic effect (referring to the amount of glucose that had to be infused during the experiment to keep the patients in a euglycemic state) (7).

Studies with both healthy subjects and subjects with diabetes have shown more rapid absorption of lispro compared to regular human insulin, ranging from 0.1 to 0.4 units/kg. Peak serum levels were seen 30–90 minutes after dosing, with bioavailability similar to that of human insulin. The mean area under the serum insulin concentration-time curve from time zero to infinity was also similar between U-200 and U-100, as was the mean peak serum insulin. The time to maximum effect was 1 hour for both formulations (8).

Human metabolism studies have not been conducted for lispro, but animal studies suggest that its metabolism is similar to that of regular human insulin (7).

Efficacy and Safety

There have been no clinical trials assessing the efficacy and safety of U-200 in volunteers with diabetes. Only one study to demonstrate bioequivalence to U-100 has been completed.

Delivery and Handling

Insulin lispro U-200 is available in a 2 × 3 mL prefilled pen (compared to 5 × 3 mL prefilled pen for lispro U-100) (7). Lispro U-100 is also available in vials (7).

The 3-mL U-200 pens can be stored unopened (not in use) at room temperature (<86°F) for 28 days. If refrigerated and unopened (not in use), they can be stored until their expiration date. If opened (in use), they may be stored at room temperature (<86°F) for 28 days. Currently, only U-100 human insulin—not U-200—has been designed for use with an insulin pump. Health care providers should always remind patients that the U-200 formulation has twice as much insulin in 1 mL as the U-100 formulation and that the dose window shows the number of units to be injected (i.e., no dose conversion is required). Patients should not transfer the product from the pen into a syringe, which can result in overdose and severe hypoglycemia (7).

Bottom Line

Although lispro U-200 shows bioequivalence to lispro U-100, no direct comparisons have been made. U-200 can be considered in patients requiring high mealtime doses of insulin.

Regular Insulin U-500

Structure

Regular insulin U-500, sold under the trade name Humulin R U-500 insulin, is a polypeptide hormone that is structurally identical to human insulin. It is formulated as 500 units/mL and has a fivefold greater concentration than regular insulin U-100. It is a clear and colorless aqueous solution composed of human insulin, glycerin, metacresol, zinc oxide, and water. With a pH ranging from 7.0 to 7.8, it may be manufactured with sodium hydroxide and/or hydrochloric acid to adjust the pH (9).

This synthesized human insulin is concentrated to allow the administration of high doses of insulin at one-fifth the volume of that of U-100 regular insulin, which holds 100 units/mL. As a more potent form of regular insulin, it is indicated for patients with type 1 or type 2 diabetes who have severe insulin resistance (defined by insulin requirements >200 units). In these patients, higher insulin requirements are limited by the largest syringes, which contain only 100 units of insulin, or insulin pens, which deliver 60–80 units per injection. The concentrated U-500 formulation bypasses the volume limitations of U-100 and improves subcutaneous depot absorption with its smaller volume. The clinical and practical implication of U-500 insulin is that it may mitigate some of the physical discomfort and barriers to adherence brought on by the need for multiple large-volume injections with its U-100 counterpart.

Pharmacodynamics and Pharmacokinetics

A single-site, randomized, double-blind, crossover euglycemic clamp trial studying the pharmacokinetics and pharmacodynamics of U-100 and U-500 insulin determined that both the overall insulin and exposure and effect of the two formulations are similar (9). The difference, however, is in the peak concentration. Although both formations have relatively long durations, the times to peak concentration and maximum effect are significantly longer for U-500 than for U-100. The greater duration of action of U-500 is thought to be affected by the absorption rate of the insulin from the subcutaneous depot. The delayed time to peak and prolonged total duration of U-500 supports the indication that it may be used appropriately in fewer multiple daily doses. The time of start of effect of U-500 is similar to that of U-100 at equal doses, indicating that it may be dosed 30 minutes before mealtime, as is indicated for U-100 (10).

Efficacy and Safety

Considering the safety and efficacy of U-500 versus U-100 regular insulin, an open-label trial examined patients with inadequately controlled type 2 diabetes who were previously taking U-100 insulin and compared the effects of twice- and thrice-daily U-500 regimens. The study's 325 patients were randomized into one of two regimen groups, and change in A1C from baseline was evaluated.

After 24 weeks, the two algorithms were found to be noninferior to each other. Beyond the clinical equivalence, both treatment regimens using U-500 produced significant reductions in A1C (thrice daily: –1.12%, twice daily: –1.22%, P <0.001 for both). Secondary endpoints included the percentage of patients achieving varying levels of A1C, differences in 7-point SMBG profiles, glycemic variability, total daily dosing, adverse effects, and hypoglycemic events. Investigators concluded that both U-500 regimens improved glycemic control and had low incidences of severe hypoglycemia and other adverse events. The results provided evidence for the safety and efficacy for both U-500 regimens, with slight favorability toward thrice-daily dosing because of lower rates of hypoglycemia.

The aim of this study was to increase understanding of multiple daily dosing regimens of U-500 that had not been studied previously. In so doing, the investigators found clinically relevant and significant reductions in A1C and shed light on the extent of the increased efficacy of U-500 compared to U-100 regular insulin (11).

Delivery and Handling

Human regular insulin U-500 is sold in vials containing 20 mL compared to the regular human insulin U-100, which comes in vials containing 10 mL. The U-500 vials are marked with diagonal brown stripes and red labels to distinguish them from vials of U-100, which have no stripes and are labeled in black (7).

Unopened U-500 vials that are not in use should be stored in a refrigerator at 35–46°F. U-500 vials that are open or in use may be kept unrefrigerated; it is recommended that they be kept in a cool environment (preferable <86°F) and away from heat and light. Opened or in-use vials must be used within 31 days or discarded. U-500 insulin should not be used if it has been frozen or if its expiration date has passed (7).

Bottom Line

Dosing errors with U-500 regular insulin can be serious and cause significant hypoglycemia. Providers must ensure that patients are well educated about how to use U-500 safely before it is initiated.

Summary and Conclusion

Progressive β-cell failure is a fundamental component of type 2 diabetes. Improved recognition and management of the cardiovascular risk factors associated with type 2 diabetes have allowed more patients to survive longer, eventually requiring exogenous insulin as part of their therapeutic regimen. Unfortunately, the growing rates of obesity among this population have also increased insulin requirements and insulin resistance. The availability of various concentrated insulin products represents a much more comfortable means of delivering large doses than through the multiple injections that would be required for large doses of U-100 insulin. Also, incorporation of these new products into pen delivery systems eliminates previous medication errors related to volume calculations.

One concern remains with the expansion of available concentrated insulins in the diabetes treatment armamentarium. Although each of the concentrated insulin products retains characteristics of the original U-100 compound, increasing doses will likely lead to increased duration of action. Therefore, patients on very high doses of concentrated insulin should be carefully monitored to guard against insulin stacking, which occurs when insulin levels build up due to repeated dosing in the absence of adequate clearance. Insulin stacking, especially when it results from an unanticipated prolonged duration of effect, may result in severe hypoglycemia.

With so many insulin products now available, it is essential that health care providers, diabetes educators, and pharmacists clearly inform patients and providers about the advantages and safety concerns with concentrated insulin and the ways in which they differ from traditional insulin products.

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Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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