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New Insulin Preparations: Potential Benefits and Risk Assessments

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ABSTRACT

Concentrated insulins have been especially problematic high alert medications. On February 25, 2015 Federal Drug Administration (FDA) approval made available insulin glargine, Toujeo® U-300 (300 units/ml) in a SoloSTAR® pen. On May 27, 2015 the FDA approved insulin lispro, Humalog® U-200 (200 units/ml) KwikPen™. Increased incidence of insulin resistant type 2 diabetes has escalated the need for concentrated insulin. This paper discusses each insulin, appropriate patient selection, benefits of the new insulins for people with diabetes and providers, and suggestions for prevention of potential off-label use of insulin pens. Counseling and assessment are essential to avoid unintended harm.

Keywords: insulin, medication errors, nurse practitioners, risk assessment, type 2 diabetes mellitus

Insulin in any form is a high-alert medication. Two new products address safety concerns related to insulin pharmacology and administration. On February 25, 2015, the Federal Drug Administration approved insulin glargine (Toujeo U-300 [300 U/mL], Sanofi-Aventis, Bridgewater, NJ) delivered subcutaneously with a SoloSTAR insulin pen.[1] Then, on May 27, 2015, the Food and Drug Administration approved insulin lispro (Humalog U-200 [200 U/mL] KwikPen, Eli Lilly and Company, Indianapolis, IN).[2] Factors motivating the development of these products include 1) the growing number of people using more than 200 units of insulin per day because of insulin-resistant type 2 diabetes (T2DM) and 2) safety issues associated with concentrated insulin dosing and administration. In response, manufacturers released these insulins in pen form only[1,3] (Toujeo and Humalog U-200) and modified the insulin pharmacokinetics and pharmacodynamics (Toujeo).[1]

The increased incidence of insulin-resistant T2DM has created a need for concentrated, long-acting, insulin with a stable action over time.[4,5] Insulin with steady bioavailability over time is characterized as having a flat time action curve. Insulin without a peak action (flat time action curve) is desired clinically in order to meet the body's ongoing physiologic need for basal (background) insulin while preventing hypoglycemia. In contrast, a steep time action curve is appropriate for bolus (meal time) insulin. Clinically, this peak of insulin action is beneficial, paralleling the increased glycemic load of a meal.

Particularly during care transitions and/or in hospital settings, patients using concentrated U-500 insulin were at increased risk for medication errors.[6,7] Reports of insulin administration errors related to the use of U-500 insulin in hospital settings are well documented.[5-8] Errors have multiple contributing factors. One factor is that U-500 insulin syringes are not available.[5,6] Instead, the person administering the insulin must convert the concentrated insulin dose for administration in a U-100 or tuberculin syringe. U-500 dosage errors occur when calculating this volume-based dose without an equivalent unit-based syringe.[6,7] Insulin dosing and administration errors created a need for a safer means of administering concentrated insulin. Adults with type 1 diabetes (T1DM) or T2DM and providers benefit from the approval of both new concentrated formulations of insulin in multiple ways.

INSULIN GLARGINE: TOUJEO U-300

Toujeo U-300 (glargine U-300) has been approved for use in adults with T1DM and T2DM.[1] Insulin

glargine substitutes Gly for 21A-Asn in its amino acid sequence,[9] creating an acid soluble solution that precipitates at physiologic pH forming a depot that slowly releases insulin glargine.[10,11] Glargine U-300 has a flatter and longer pharmacokinetic and pharmacodynamics profile than glargine U-100.[9,12] Clinically, these characteristics prevent basal insulin gaps and hypoglycemia. Glargine U-300 users experienced fewer hypoglycemic episodes (14% reduction overall and 31% reduction in nocturnal hypoglycemia)[13,14] and less weight gain.[9] Adults with T1DM using glargine U-300 had fewer glycemic fluctuations as measured with continuous glucose monitoring than those using glargine U-100.[15] This finding demonstrates benefit for all basal insulin users. Once daily subcutaneous injections of glargine U-300 may take up to 5 days to reach a steady state.[1] This longer time to a steady state is one reason Toujeo is not indicated for use in diabetic ketoacidosis.[1] Currently, the cash price of Toujeo (glargine U-300) is approximately $0.27 per unit.[16] This cost is about $0.53 more per 1,000 units than glargine U-100.[16,17] Coupons and copay discounts are available and were not considered in this calculation. Price information varies widely and is available at sites such as www.drugs.com. Full prescribing information is available at https://www.toujeopro.com/dosing-and-administration.

INSULIN LISPRO: HUMALOG U-200

Humalog U-200 (lispro U-200) is bioequivalent to Humalog U-100 (lispro U-100) and approved for adults with T1DM and T2DM.[3] The pharmacokinetics and pharmacodynamics of Humalog U-200 are unchanged from those of Humalog U-100.[3] Both concentrations are administered 15 minutes before or immediately after a meal. A patient education sheet is available at http://pi.lilly.com/us/humalog-u200-ppi.pdf. Although Humalog U-100 is available in vial or KwikPen, the Humalog U-200 formulation is available only in the KwikPen.[3] The cash price of the Humalog U-100 KwikPen is around $0.31 per unit.[18] The cash price of Humalog U-200 with a discount coupon ranges from $0.26 per unit to $0.37 per unit.[19] The Humalog U-200 KwikPen averaged around $9.95 more for 1,000 units than the Humalog U-100 KwikPen. However, prices vary widely, and erroneous online pharmacy information was common (eg, Humalog U-200 KwikPen is packaged with 2 pens not 5[19]).

INSULIN PEN

Thin pen needles create challenges for high-volume insulin administration by increasing the time it takes to deliver the insulin dose.[20] Removing the pen too soon during insulin administration reduces the insulin delivered by the pen.[20] A more concentrated (lower volume) insulin delivered by the pen decreases insulin administration time and may decrease the incidence of insulin underdelivery caused by early needle removal. One injection with the SoloSTAR pen delivers up to 80 units of glargine U-300. The glargine U-300 dose is equivalent to a glargine U-100 dose with a third of the insulin volume.[9] The KwikPen delivers up to 60 units of lispro U-200 with half the insulin volume of the U-100 pen.[3] Both pens are calibrated by 1-unit increments.[1-3]

DOSING

Concentrated insulin (eg, U-500) has been available since the 1950s.[8] Understanding insulin concentrations is key when prescribing and counseling patients. U-100, U-200, and U-300 describe the number of units in 1 mL insulin. It is a ratio used to convey concentration. For example, 1 mL U-200 insulin contains 200 units, whereas 1 mL U-300 insulin contains 300 units. The subcutaneous delivery of U-200 and U-300 insulins with an insulin pen is an innovation designed to prevent dosing errors. Manufacturers[1,3] have engineered the pens' mechanism to control the volume that each unit marking on the pen delivers to the person with diabetes. Fifty units of a U-100 insulin equals 0.5 mL insulin. However, 50 units of a U-200 insulin administered with a pen delivers half that volume (0.25 mL) of insulin, with a similar efficacy to the 50-unit U-100 insulin dosage. Previously prescribing a concentrated insulin required translation of the dose for delivery with a U-100 or tuberculin syringe. For current U-100 insulin users, the prescriber simply orders the same number of U-200 or U-300 units, and the pen mechanism converts the volume.

A basal insulin, glargine U-300, is dosed subcutaneously at a consistent time once daily. First calculate the total daily insulin dose for an insulin-naive client as 0.2 to 0.4 units of insulin/kg. Then, prescribe one