JNP

Expanded Basal Insulin Options for Type 2 Diabetes Mellitus

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ABSTRACT

Basal insulin is a component of therapy for many patients with diabetes mellitus. Several concentrated basal insulins are newly available. Nurse practitioners should be aware and informed of the various concentration options as they manage their patients. This article reviews the available concentrated products with a focus on degludec insulin. Nurse practitioners should be knowledgeable of the resulting safety considerations, particularly during transitions of care, or conversions between products.

Keywords: basal insulin, concentrated insulin, insulin degludec, insulin glargine, U-500 insulin

Diabetes mellitus (DM) is a chronic condition characterized by hyperglycemia and other metabolic disturbances. It is estimated that 9.3% of the American population has DM, and it is the seventh leading cause of death.[1] The majority of individuals have type 2 DM, which results from insulin resistance and relative insulin deficiency from beta-cell dysfunction. Uncontrolled DM may lead to microvascular and macrovascular complications. The management of type 2 DM involves a patient-centered approach with lifestyle modifications to reduce cardiovascular risk factors and minimize complications. Individualized treatment goals are based on patient and disease factors including risks for hypoglycemia, life expectancy, and comorbidities.[2,3] Although a variety of oral and injectable therapies are available, type 2 DM is progressive, and many individuals will require insulin therapy. Of almost 21 million adults reported to be using medication for diabetes, 28.7% were receiving insulin as monotherapy or combination therapy.[1]

Basal insulin is the most convenient initial insulin regimen, and it most closely mimics physiologic insulin patterns by providing continuous glucose control throughout the day.[3] Clinical practice guidelines recommend the initiation of basal insulin in individuals with symptomatic hyperglycemia with a glycosylated hemoglobin (A1c) value > 9%[2] or > 10%.[3] Historically, long-acting insulin was developed by adding modifiers to shorter-acting regular insulin, such as protamine in neutral protamine Hagedorn (NPH) insulin. With an average peak action of 12 hours, NPH is typically dosed twice daily. Longer-acting insulin analogs including glargine and detemir provide constant peakless concentrations with long enough duration in some individuals for once daily dosing. The analogs and NPH have shown similar efficacy in terms of A1c lowering. However, some experts express preference for the newer analogs given their lower potential for hypoglycemia.[2] With education, NPH insulin can be used safely for many patients at a much lower cost.[3,4]

Basal insulins were previously only available in a single standard concentration of 100 U/mL (U-100). Many individuals with type 2 DM have insulin resistance necessitating doses of at least 200 units daily, which requires multiple injections of standard insulins. More concentrated basal insulins were developed to help improve absorption and minimize larger injection volumes. This review discusses currently available options for basal insulin, including the standard and more concentrated insulins, and resulting safety considerations during transitions of care or conversions between products. It focuses on insulin degludec, the first ultra—long-acting basal insulin.

OLDER BASAL INSULINS AT STANDARD CONCENTRATIONS

Basal insulin formulations developed by modifying regular shorter-acting insulin have been available since the 1930s; however, NPH is the only one currently used. The properties of selected U-100 basal insulins including the newly available insulin degludec are described in Table 1. Several are also available in premixed combinations with shorter-acting/prandial insulins.

Given its duration of action of up to 24 hours, NPH is classified as an intermediate-acting insulin. When injected subcutaneously, its onset of action is 1.5 hours with peak effects at 4 to 6 hours. The exact mechanism of insulin disassociation is not well-defined, which potentially leads to varied pharmacokinetics (PK.) That and the concern of the peaks and troughs with NPH leading to an increased risk of hyper- and hypoglycemic events led to the development of analogs with more predictable PK properties. Several studies have been conducted to see if these structural modifications would result in improved safety and efficacy. A systematic review of 28 randomized controlled trials comparing insulin glargine with other insulins including NPH (11 studies) and insulin detemir (4 studies) was performed.[11] Investigators established a primary end point of a target A1c level $\leq$ 7% without hypoglycemia with key secondary end points including a reduction in A1c, the percent of patients achieving target A1c, and risk of hypoglycemic episodes. For the primary end point, no difference was found between insulin glargine and NPH in overall or symptomatic hypoglycemia, but fewer events of nocturnal hypoglycemia were observed with insulin glargine. When considering overall events of hypoglycemia, a similar trend was observed. No differences were noted with HbA1c reduction between formulations. An advantage in the primary end point was observed with insulin glargine compared with insulin detemir with overall hypoglycemia, but no differences were observed with symptomatic hypoglycemia. Overall efficacy favored insulin glargine compared with insulin detemir only for those studies in which participants were using concomitant bolus insulin in addition to analog insulin and oral therapies.[11]

A 5-year randomized trial directly comparing insulin glargine with NPH was conducted in 984 patients. By the end of the study, approximately 60% of patients in both groups were receiving bolus insulin in combination with basal insulin and oral antidiabetic agents. A number needed to harm of 25 was determined, indicating that if 25 patients were treated with NPH instead of glargine for 5 years, then 1 patient would experience an episode of severe hypoglycemia.[12] Severe hypoglycemia was defined as requiring third-party assistance and either prompt recovery after carbohydrate or glucagon administration, or serum glucose $\leq$ 56 mg/dL. Findings for all symptomatic hypoglycemic events or nocturnal hypoglycemia were not statistically significant.[12]

In summary, several systematic analyses confirm that NPH and the insulin analogs are likely clinically similar with respect to individual patient A1c-lowering effects. Risks of hypoglycemia appear to be higher with NPH, although overall rates are low.

Table 1. Selected Standard 100-U/mL Basal Insulins[5-10]

	NPH	Glargine	Detemir	Degludec
Brand name(s)	Humulin N Novolin N	Lantus	Levemir	Tresiba
Duration of action (hours)	24	Up to 32	Up to 24	42
Typical frequency of administration	Twice daily	Once or twice daily	Once or twice daily	Once daily
Pregnancy category	B	No human studies	B	C
Available forms	Vial, Pen (Humulin N KwikPen)	Vial, Pen (Solostar)	Vial, Pen (FlexTouch)	Pen (FlexTouch)
Estimated cost (per 100 units)[a]	$15.35 ($32.54 for pen)	$29.82	$32.28	$35.50

NPH = neutral protamine Hagedorn.

[a] Unless otherwise noted, estimated cost per unit is similar between pen and vial.