

## Basal Insulin—Myths and Realities

a report by

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The era of strict diabetes control requires a timely use of insulin. While there are many types of insulin available and sometimes difficulties in understanding the differences among those in that specific category, it is essential to be well aware of how basal insulin works, the possible differences and advantages, disadvantages, and cost. Patients with type 1 diabetes will require basal insulin from day one in combination with fast-acting insulin; patients with type 2 diabetes with very high fasting glucose levels will also require a dual insulin (basal plus fast-acting or premix insulin). Basal insulin in combination with oral agents may suffice to achieve today's new glucose goals early in type 2 diabetes when endogenous insulin production has not been extensively impaired.

### Basal Insulin

Ideal basal insulin should be one that has a 24-hour profile that is flat and peak-less.

In addition, insulin should be reproducible from day to day with very little inter- and intra-patient variability and with little or no immunogenicity. It should also limit lipolysis and excessive hepatic glucose output in order to prevent early morning hyperglycemia (loss of control or Dawn phenomenon).

### Human Basal Insulin

While there are animal sources (beef, pork and combination of beef/pork), as well as human semi-synthetic sources (from pork insulin) there is very little use of animal source insulin in the US today.

The oldest basal insulin in use today is neutral protamine hagedorn (NPH), which is human insulin in solution with protamine that allows the insulin a longer duration and a peak effect of four to six hours after subcutaneous injection. What is most important with NPH insulin is the patient education process, where the patient must remember to resuspend the insulin prior to administration to avoid errors with dosing and action. The total duration of action varies

by dose; the smaller the dose the shorter the duration and the higher the dose the longer the duration. In simple terms, as more insulin is administered, the action curve moves further to the right.

However, there are advantages to NPH: it can be mixed in the same syringe with regular insulin, as well as mixed with fast-acting analogs. It is not recommended as a once-a-day insulin in patients with type 1 diabetes.

Lente and ultralente insulin is rarely used today. They were made by using zinc in regular insulin with an acetate buffer, thus making an insulin that dissolves poorly once injected in the subcutaneous tissue. The profile of lente and ultralente insulin was less predictable than NPH and had similar problems with duration based on total dose.

In a quest to improve basal insulin delivery, insulin analogs were developed using recombinant DNA technology. The optimal basal insulin properties should include once-daily dosing, low intra-patient variability, and a high consistency of time action profile.

The first basal insulin available for clinical use was insulin glargine, with amino acid changes in both the alpha and beta chains of the insulin molecule and a lower pH. While glargine results in a relatively constant release, and it appears to have less variability than NPH, it is not yet the perfect basal insulin. The mean duration of glargine is 22+/-4 hours but there are still inter- and intra-patient variability.

The newest basal insulin on the market is insulin levemir, an analog soluble with a neutral pH with acylation with myristic acid (fatty acid chain) in position 29 of the beta chain.

Studies with all basal insulins in a treatment-to-target approach have resulted in similar A1c levels at the end of the study. Therefore, with regard to achieving targets there is no difference if insulin is titrated properly.

Differences are reported in areas such as hypoglycemia. The new basal insulin analogs have shown a decrease in hypoglycemic episodes, glargine less than NPH, and detemir less than glargine.

Consistency of blood glucose response was studied most recently by Heise and showed that variability exists with all basal insulin, but the most glucose variability resulted with NPH and the least with levemir.

The quest for the best basal insulin will continue; but what we know today is that insulin is better than no insulin and that insulin, when properly titrated, can get patients to target. Ultimately, we must take into consideration secondary advantages and disadvantages as discussed before and factor cost into the equation.

The most important message is that we have choices for basal insulin, and we can make decisions and adjustments based on individual needs. Some patients

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Weight gain has been observed with all types of insulin and is usually based on per cent decrease of A1C, (2.5Kg per 1% decline).

It appears that weight gain can be less with levemir insulin.

may do better with one type of insulin than another and, at the end of the day, our aim is to treat our patients to target and to initiate insulin therapy on a timely basis. To delay initiation of insulin only hurts the patient. ■

#### **Further Reading—Recent Articles of Interest by Jaime Davidson, MD, FACP, FACE**

Leiter L A, Ceriello A, Davidson J A, Hanefeld M, Monnier L, Owens D R, Tajima N, Tuomilehto J; International Prandial Glucose Regulation (PGR) Study Group, "Postprandial Glucose Regulation: New Data and New Implications", *Clin Ther* (2005);27 Suppl 2: pp. S42–56.

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Davidson J A, Perez A, Zhang J; The Pioglitazone 343 Study Group, "Addition of Pioglitazone to Stable Insulin Therapy in Patients with Poorly Controlled Type 2 Diabetes: Results of a Double-blind, Multicentre, Randomized Study", *Diabetes Obes Metab* (2006);8(2): pp. 164–174.