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Are New Insulins Just a Breath Away?

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A great deal of progress is being made in the area of insulin therapy. The goal of these new therapeutic approaches is to address three distinct needs: 1) the need for so-called "warp-speed insulins" as an improvement over rapid-acting formulations, 2) the need for a more efficient, long-acting basal insulin, and 3) the need to reduce or eliminate the use of needles.

Michael Weiss, MD, PhD, Case Western Reserve University, Cleveland, OH, explained the medical need of "warp-speed" (ultrarapid absorption) insulin. "Warp-speed insulins" may mimic first-phase insulin secretion more efficiently to prevent immediate postprandial hyperglycemia. Additionally, they may reduce late postprandial hypoglycemia and the pharmacokinetic (PK) variability that is currently observed within and between patients.

The technical hurdle to achieving these goals is to stabilize the aggregate form of insulin prior to administration while at the same time ensuring rapid dissociation of injected hexameric complex to the therapeutically active insulin monomer. Methods to achieve rapid absorption have included delivery systems (microneedle patch), chemical accelerants (EDTA/citrate; VIAject), the use of an enzymatic environment (hyaluronidase co-injection), and protein engineering [Forst T et al. *Diabetes Care* 2010; Muchmore DB et al. *J Diabetes Sci Technol* 2010; Weiss MA. *Vitam Horm* 2009].

Dr. Weiss's work at Case Western focuses primarily on this last approach, with the practical aim of not only producing a more rapid onset of action but also developing a temperature-stable insulin molecule that could be distributed in areas that lack refrigeration, such as in underdeveloped nations. His work using an amino acid linker technology has yielded lead compounds that do not rely on zinc (contrary to other preparations) and are stable over several days at room temperature [Hua QX et al. *J Biol Chem* 2008]. Investigations that concern these types of compounds are ongoing.

Slow-Release Insulin

Satish K. Garg, MD, University of Colorado, Denver, CO, reviewed pipeline candidates of slow-release insulin. While acknowledging the currently available treatment options of insulin glargine and insulin detemir as viable choices for long-acting basal coverage, the development of next-generation compounds is necessitated by the need for a "true" 24-hour therapeutic effect with less hypoglycemia and better A1C control and without the potential for weight gain. Novel candidates include degludec, basal insulin therapy, "smart" insulin, and the transdermal insulin patch.

Degludec is a recombinant human insulin with a single-base deletion and an added 16-carbon fatty acid moiety. Degludec forms soluble multihexamer assemblies after subcutaneous injection. In the first of three studies that were reported at the American Diabetes Association 70th Annual Scientific Session 2010, degludec demonstrated equivalent duration with less glycemic variation compared with insulin glargine (IGlar) in a euglycemic clamp investigation [Jonassen IB et al. ADA 2010 Abstract #0039].

A second study that compared degludec and IGlar in combination with insulin aspart in type 1 diabetes mellitus (T1DM) patients showed that at 16 weeks, degludec was similar to IGlar with regard to glycemic control. However, degludec demonstrated superiority over IGlar for incidence of hypoglycemia (RR, 0.72; 95% CI, 0.52 to 0.99; n=177) [Luigi F et al. ADA 2010 Abstract #0559-P].

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A similar study, looking at activity in T2DM patients with both comparators taken in combination with metformin (n=122), also showed similar glucose control. There was a nearly 50% reduction in hypoglycemic episodes for degludec versus IGlar (RR, 0.44; 95% CI, 0.15 to 1.25) [Zinman B et al. ADA 2010 Abstract #0040]. Phase III trials for this compound are ongoing.

Smart insulin refers to ongoing efforts to develop a compound that is able to sense and respond to glycemic levels in the body. The molecular technique is based on insulin with built-in pairs of boronates and polyols that can produce soluble high-molecular-weight self-assemblies under control by carbohydrates [Hoeg-Jensen T et al. *J Am Chem Soc* 2005]. This approach is currently entering Phase I trials.

New (Old) Delivery Systems

William Cefalu, MD, Pennington Biomedical Research Center, Baton Rouge, LA, reviewed recent findings for insulin formulas that are being tailored to perform in noninjection delivery systems. The rationale for such efforts is that alternative insulin delivery has the potential to increase compliance while inducing better metabolic control. The possible routes of administration are nasal, sublingual, buccal, oral, inhaled, and intraperitoneal.

The challenges of the intranasal approach are the need for a permeability enhancer, low bioavailability, and nasal irritation. Benefits include rapid onset of action and a significant reduction in postprandial glycemia ($p<0.001$) [Coates PA et al. *Diabet Med* 1995]. A recent study that evaluated the pharmacokinetics of nasal insulin demonstrated that an ultrarapid-acting intranasal insulin formulation was effective at varying concentrations (0.7% and 1% concentration) and that dose flexibility was feasible. A dose response was observed, as measured by baseline-adjusted maximum concentration C(max) of 22, 27, 56, 62, and 84 muU/ml for the 25-, 35-, 50-, 70-, and 100-U doses ($p<0.0001$), respectively, and by baseline-adjusted area under the curve (AUC; 0-45 min) values of 491, 592, 1231, 1310, and 1894 muU/ml/min ($p<0.0001$) [Stote R et al. *J Diabetes Sci Technol* 2010].

Biopotency for intranasal insulin was confirmed in a study that compared intranasal insulin and the oral insulin lispro in T1DM patients [Stote R. et al. ADA 2010 Abstract #520-P]. However, a Phase II investigation of intranasal insulin + oral therapy versus oral therapy alone in T2DM subjects failed to meet the primary endpoints of a 0.7% mean reduction in HbA1C and mean reduction in 2-hour postprandial blood glucose of at least 20 mg/dL (n=90). A follow-up study that used CGM to control for uneven data contribution throughout the course of a day did show significant efficacy ($p<0.001$), though current development of this method awaits partnering [CPEX Pharmaceuticals. AACE Meeting 2010].

The buccal route of administration takes advantage of the mucosal area in the back of the throat. Though this tissue is not amenable for peptide transport, buccal insulin uses a microfine preparation of encapsulated insulin micelles to overcome the barrier. Biopotency of buccal insulin therapy was demonstrated in 2005, and equivalence to subcutaneous insulin was shown in a small study in 2007 [Guevara-Aguirre B et al. *Diabetes Technol Ther* 2007]. Phase III trials of this insulin strategy in T1DM are ongoing.

Oral insulin appears to be the most attractive to patients. However, this approach has the most physiological barriers to overcome, and multiple formulations with liposomes, protease inhibitors, and absorption promoters have been attempted [Dhawan S et al. *PharmTech* 2009]. New formulations that have demonstrated proof of principle have recently emerged [Kapitza C et al. *Diabetes Care* 2010; Heinemann L et al. *J Diabets Sci Technol* 2009]. An insulin conjugate molecule, IN-105, is currently in a Phase III study.

In a small study that was highlighted at the ADA 2010, an oral insulin demonstrated proof of principle and the ability to be effective, irrespective of timing of meals, in T1DM [Eldor R et al. ADA 2010 Abstract #521]. Additionally, the development of a hepatic-directed vesicle oral insulin that targets the liver in an attempt to restore the liver's key function of storage/release of glucose is currently underway. Proof of principle has been demonstrated, and a Phase IIB trial was recently completed [Schwartz S et al. *Diabetes* 2009].

Dr. Cefalu closed with a review of data for inhalable insulin therapies. Using an insulin particle of 2-5 microns, an inhaled insulin is able to penetrate deep into the lungs, where it is rapidly absorbed. In a large dataset that was presented at ADA 2010, T2DM subjects were randomized to either prandial inhaled insulin plus bedtime insulin glargine or twice-daily biaspart insulin for 1 year (n=667). The safety and tolerability profile was similar for both treatments. However, those who received inhaled insulin plus glargine demonstrated an increased occurrence of cough and change in pulmonary function [Rosenstock J et al. *Lancet* 2010].

Regarding safety, inhaled insulin was superior to biaspart insulin for total incidence of hypoglycemia ($p<0.0001$), and the formation of antibodies, though observed, did not appear to impact glucose control [Rosenstock J et al. *Lancet* 2010; Rosenstock J et al. *Diabetes* 2006]. Effect on FEV_1 was reported as "slight" initially and nonprogressive over time [Petrucci R et al. *Diabetologia* 2009]. Patients also exhibited less weight gain with inhaled insulin versus subcutaneous insulin [Rosenstock J et al. *Diabetes* 2006].