Technosphere Inhaled Insulin: Is Faster Better?

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Pulmonary-delivered insulin is again a reality (1). The failure of the first inhaled insulin in 2007 showed that being radically different from what health care providers are used to, even when injections are avoided, can be problematic. The current product Technosphere inhaled insulin has addressed many of the prior concerns—a more convenient delivery device that is dosed in insulin units. Also, fear of lung toxicity or tumor development has been lessened somewhat by in vitro cytotoxic (2) and in vivo clearance (3) studies, plus a 2-year clinical trial showed no differences in pulmonary imaging or function in Technosphere-treated and untreated subjects with diabetes (4). In addition, aerosolized medicines that have effective absorption into the bloodstream are well established (5), with numerous agents having been tried including glucagon-like peptide 1 (6).

A highly touted feature of pulmonary-delivered insulin is its *rapid* absorption—peak absorption by 10–15 min and fully cleared by 2–3 h versus a peak of 45–60 min and clearance of 5–6 h for injected analog prandial insulins (1,7) (Fig. 1). The potential importance of an ultrafast "on response" relates to the phasic nature of endogenously secreted insulin. An intravenous glucose infusion in humans without diabetes elicits a distinct first phase of insulin secretion over the first 10 min that is followed by a short lull and then a sustained second phase for the duration of the hyperglycemia. Actually, the diverse nutrient makeup of meals and their oral delivery initiate a more broad-based insulin response that does not separate into distinct phases. Still, the early insulin that is secreted into the portal vein serves a key role to rapidly turn off hepatic glucose production (8) and likely contributes to the fall in glucagon and controlled rise and fall in circulating free fatty acids that collectively characterize normal prandial metabolism. A defining feature of type 2 diabetes is a near-total absence of the early insulin response, while the later phase is present and often exaggerated because of the hyperglycemia, i.e., mealtime insulin is delayed (9,10). Restoring early insulin with a short-term insulin infusion in type 2 diabetes markedly improved prandial glycemia and lipemia (11). Hence, a reasonable conclusion is the earliest secreted insulin is a necessary element of the normal mealtime insulin response, and consequently optimal exogenous prandial insulin needs a rapid "on response." And Technosphere insulin is the best we have. However, a question that needs to be answered is whether that difference provides any meaningful clinical advantage over the injected prandial insulins.

Two studies in this issue of *Diabetes Care* provided insight into how this insulin performs. Bode et al. (12) performed a 24-week noninferiority open-label study of subjects with type 1 diabetes that received injected basal and aspart insulins (basal-bolus) or injected basal and inhaled Technosphere insulin at meals. The main finding was noninferiority with the attained A1C values falling within the agreed-upon study criteria of within 0.4%. The basal-bolus group fell from 7.9% after basal insulin optimization to 7.5% at the end of the study versus 7.9% to 7.7% in the inhaled insulin group. However, the percent of subjects attaining A1C $\leq$7% was superior in the injection group (31% vs. 18%), and the 7-point glucose profiles showed better control in the injected insulin group at all times except fasting. Otherwise, there were no major surprises or concerns over the use or safety of inhaled insulin.

Thus, for type 1 diabetes, the fact that inhaled insulin was not more effective than prandial injections and probably less effective (despite meeting the noninferiority criteria) seems predictable as the rapid insulin profile likely runs out too soon on the background of complete insulin deficiency. However, features of inhaled insulin raise novel possibilities that might allow for creative ways to take advantage of its unique action profile. Importantly, Bode et al. found the faster "off time" of inhaled insulin lowered the risk of hypoglycemia 2–5 h

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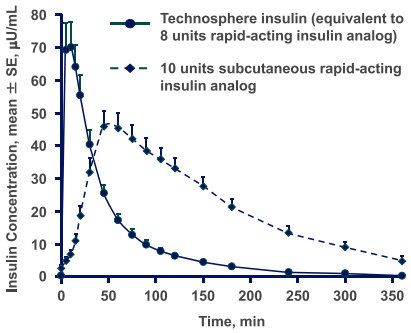

Figure 1—Pharmacokinetic profiles (mean ± SE) of inhaled Technosphere insulin and subcutaneously injected rapid-acting insulin analog insulin presented by Cassidy et al. at the 69th Scientific Sessions of the American Diabetes Association, New Orleans, LA, 5–9 June 2009. Reproduced from Boss et al. (7).

after a meal versus the injected prandial insulin. As such, second inhalations 90–120 min after meals, as discussed elsewhere (7), could be a powerful strategy for fine-tuning mealtime insulin coverage while minimizing the risk of hypoglycemia, especially if used with continuous glucose monitoring. A second intriguing possibility is using inhaled insulin together with injected prandial insulin to get an early insulin boost. Technosphere insulin added at the start of a meal with a closed-loop pump system has been shown to result in superior mealtime glycemic control (13,14).

The study by Rosenstock et al. (15) is a 24-week comparison in subjects with type 2 diabetes poorly controlled with oral antidiabetes agents of adding mealtime Technosphere inhaled insulin or a placebo inhalation (the Technosphere matrix fumaryl diketopiperazine) to their usual antidiabetes medications, which were mostly metformin or sulfonylurea and metformin. Thus, a notable aspect of this study is inhaled insulin without basal insulin—a true injection-free program. The main finding was as expected—a statistically superior lowering of A1C with the inhaled insulin from baseline 8.3% to 7.4% versus to 7.8% with the Technosphere placebo. There was also a modest doubling of nonserious hypoglycemia with the inhaled insulin, mostly in sulfonylurea-treated patients. These findings support a smaller, shorter study with a similar protocol (16).

Remembering that the principal prandial insulin secretory defect in type 2 diabetes is a delayed mealtime response (9,10), one might have hoped for an even lower A1C with the inhaled insulin. Studies with injected prandial insulin alone in type 2 diabetes have shown better A1C values, but with considerably more hypoglycemia (17,18). However, a striking finding in the study by Rosenstock et al. (15) is the 7-point glucose profile: inhaled insulin did a good job at controlling the postmeal values, although a caveat is that the testing was done 90 min after starting the meal, before the insulin effect is over. Failure to see a lower A1C value was shown to be because of no appreciable impact of the inhaled insulin on fasting blood glucose.

Thus, a key question is whether a combination of properly titrated inhaled insulin and injected basal insulin would produce a superior and safer approach than injected basal-bolus insulin in type 2 diabetes. This is reminiscent of how the combination insulin and glucagon-like peptide 1 receptor agonist story evolved—similar overall blood glucose control from different patterns of improvement when twice-daily exenatide (postprandial) and glargine insulin (fasting and premeal) were used individually (19) but amazing glycemic control when used together (20). So far there is insufficient evidence to know what to expect from the combination of Technosphere insulin and injected basal insulin. A 52-week study of glargine insulin and Technosphere inhaled insulin used together lowered A1C from 8.7% to 8.0% (21). In contrast, A1C values in a study of injected basal-bolus insulin fell from 8.1–8.3% to 6.5–6.7%, but with substantial weight gain and hypoglycemia (22).

In summary, the ultrafast profile of inhaled Technosphere insulin is novel and brings several possibilities. Of particular interest is intensive mealtime insulin coverage with less hypoglycemia through repeat doses or if used with injected prandial insulin. However, these possibilities are more speculative than proven. As such, inhaled insulin is still a convenience product rather than a proven advance in insulin therapy. However, it is at the forefront of several faster insulins that are in development (22,23). And the question remains—is faster better?

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

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