

Prandial Insulin: Is Inhaled Enough?

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ABSTRACT The low proportion of patients achieving glycemic targets is well documented for both type 1 and type 2 diabetes. Postprandial glucose levels are often not monitored but contribute significantly to total glycemic burden. Prandial rapid-acting insulin analogues were introduced to address some of these problems but still do not provide a physiologic insulin replacement. Inhaled prandial insulins have been developed to free patients from multiple mealtime injections and make intensive insulin regimens more acceptable. Several inhaled formulations of prandial insulin are in development but differ significantly with respect to inhaler characteristics and pharmacokinetic profiles. This brief review summarizes the properties of the new prandial inhaled insulins and discusses how postprandial glycemic control is dependent not only on the insulin dose, but also on the pharmacokinetic characteristics of insulin delivery. There is no antihyperglycemic agent with a glucose-lowering effect superior to that of insulin; new prandial products that improve coordination between insulin availability and meal absorption and are more acceptable to patients may increase the proportion of diabetic patients achieving and maintaining glycemic targets. *Drug Dev Res* 69:138–142, 2008. ©2008 Wiley-Liss, Inc.

Key words: type 2 diabetes; prandial insulin; inhaled insulin; Technosphere[®] Insulin; Exubera[®]; glycemic control

INTRODUCTION

Landmark clinical trials in both type 1 and type 2 diabetes have clearly demonstrated that intensive antihyperglycemic therapy with insulin will delay, prevent, or reduce the microvascular and macrovascular complications that seriously impact morbidity and mortality [Gaede et al., 2003; Martin et al., 2006; Nathan et al., 2005; UK Prospective Diabetes Study (UKPDS) Group, 1998; Writing Team for the Diabetes Control and Complications Trial, 2003]. There is no antihyperglycemic agent with a glucose-lowering effect superior to that of insulin [Riddle, 2005]. The goals of intensive therapy with insulin are two-fold: (1) to replicate normal insulin physiology, including a rapid onset and a limited duration of action at meal time; and (2) to ensure basal insulin support over a 24-h continuum. The relative importance of postprandial control increases as HbA1c levels approach the targets set by the American Diabetes Association (<7%),

American Association of Clinical Endocrinologists ($\leq 6.5\%$), and European Association for the Study of Diabetes ($\leq 6.5\%$) [Nathan et al., 2006]. However, the early initiation and widespread use of prandial insulin is hampered by the inability of existing prandial insulins to mimic physiologic insulin release and reluctance on the part of physicians and patients to initiate prandial injections.

Subcutaneously injected insulins have several drawbacks. A relatively slow systemic absorption produces a delayed onset of action while the metabolic effect exceeds the postprandial spike in blood glucose,

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thereby increasing the risk of late postprandial hypoglycemia. The development of rapid-acting insulin analogues (RAAs) has been an attempt to address these issues, but current formulations still fall short of simulating early physiologic insulin release [Plank et al., 2005].

Novel inhaled insulins for prandial dosing have been introduced to facilitate postprandial glycemic control. Exubera[®] is a recently approved inhaled insulin with up to 7 years of patient exposure. Clinical development is underway for inhaled AERx[®] (Novo Nordisk A/S), AIR[®] (Alkermes; Eli Lilly), and Technosphere[®] Insulin (MannKind Corporation). However, their characteristics as prandial insulins differ. The pharmacodynamic profiles for AIR[®], AERx[®], and Exubera[®] are similar, while that of Technosphere[®] Insulin differs considerably [Heinemann and Heise, 2004].

TECHNOSPHERE[®] INSULIN INHALATION SYSTEM

The Technosphere[®] Insulin Inhalation System (herein described as TI) has been developed as a prandial insulin with the closest approximation to date of normal post-meal insulin physiology. TI is delivered through single-dose cartridges in a discreet hand-held device and has been optimized for inhalation into the deep lung. TI consists of recombinant human insulin adsorbed onto a proprietary novel excipient that self-assembles into Technosphere[®] particles. The insulin-loaded particles dissolve rapidly in the physiological pH of the lung and insulin is absorbed into the systemic circulation, with a time to maximum concentration (t_{max}) of approximately 15 min. As a result of the rapid absorption, the metabolic effect of TI peaks substantially earlier than has been reported for other insulin formulations, whether injected or inhaled [Rave et al., 2007c]. In clinical studies, the majority of the glucose-lowering activity of TI is delivered in the first 3 h post-dose, mitigating the risk of late postprandial hypoglycemia [Rave et al., 2007b]. Similarly, in healthy individuals, two-thirds of the meal-related insulin secretory response occurs during the first and second hours post-meal, corresponding to the appearance of glucose in the circulation [Polonsky et al., 1988].

Absorption

In a study of healthy subjects, the pharmacokinetics of 100 U of TI (TIU) and 10 IU subcutaneous (s.c.) regular human insulin (RHI) were compared [Boss et al., 2004; Pfitzner and Forst, 2005]. One hundred TIU demonstrated a very rapid absorption, with a mean t_{max} of 13 min and a mean maximal concentration (C_{max}) of 371 μ U/mL. In contrast, the mean t_{max} for 10 IU of s.c. RHI was 121 min, with a

mean C_{max} of 34 μ U/mL. The difference in t_{max} between TI and s.c. RHI provides an explanation for the more rapid onset of metabolic action with TI (Fig. 1; see also Fig. 3). Clinical doses of TI provide maximal plasma insulin concentrations that are significantly higher than levels achievable with any other insulin to date (see below for Exubera[®] and AIR[®]). In addition, TI provided a bioavailability of 26% relative to s.c. RHI (based on cartridge dose).

Pharmacodynamics

The effectiveness of TI and s.c. RHI have been compared in a cross-over study in subjects with type 2 diabetes [Rave et al., 2007c]. During the trial, subjects continued their usual basal insulin (as taken prior to study entry). Following a meal challenge, serum insulin peaked at a median of 15 min post-dose for 48 TIU, while for s.c. RHI (14 IU) there was a broad insulin peak over approximately 90–120 min post-dose. The maximal serum insulin concentration was 45% greater with TI. The total insulin exposure over the 4-h study period was nearly identical for TI and s.c. RHI. However, there was a 40% lower maximal postprandial glucose excursion in the TI group as compared with s.c. RHI. In addition, total glucose exposure was almost 50% lower with TI than with s.c. RHI (Fig. 2). This demonstrates that postprandial glycemic control is dependent not only on the insulin dose, but also on the pharmacokinetic characteristics of insulin delivery.

Time-Action Profile

The postprandial pharmacodynamics of TI vs. s.c. RHI has been assessed with an isoglycemic glucose-clamp study in subjects with type 2 diabetes [Rave et al., 2007b]. The distribution of the total glucose-lowering effect was significantly different between TI (48 TIU) and s.c. RHI (24 IU) ($P < 0.05$). The adjusted mean time to maximal glucose-lowering effect

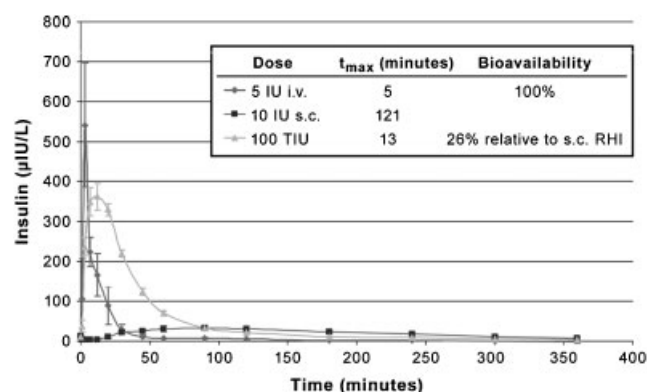


Fig. 1. Absorption profile of 100 TIU Technosphere[®] Insulin and 10 IU of s.c. regular human insulin over time in healthy volunteers.

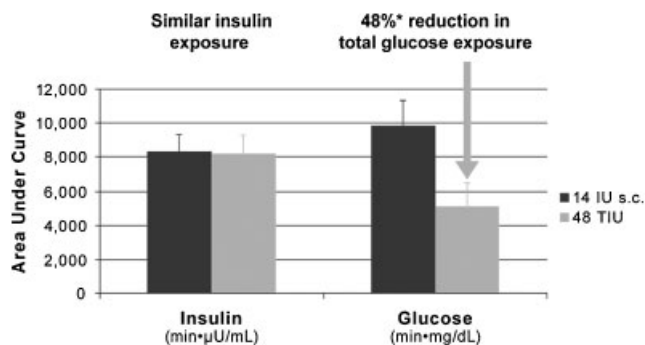


Fig. 2. Postprandial glucose exposure is reduced with Technosphere[®] Insulin versus s.c. regular human insulin in a meal-challenge study conducted in patients with type 2 diabetes.

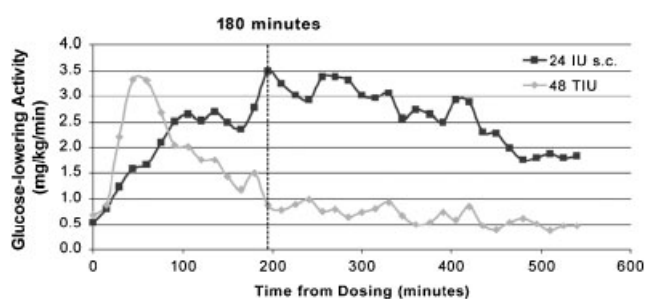


Fig. 3. Glucose-lowering activity over time with Technosphere[®] Insulin and s.c. regular human insulin in a glucose-clamp study conducted in patients with type 2 diabetes. The majority of the glucose-lowering effects of Technosphere[®] Insulin occurred in the first 180 min post-dose, while the glucose-lowering effects of s.c. RHI occurred over many hours.

(GIR- t_{max}) was approximately 200 min earlier with TI than with sc RHI ($P < 0.0001$). The majority (71%) of the total glucose-lowering effect of TI was delivered during the 0–3-h post-dosing period, compared with only about 27% of the total effect of s.c. RHI (Fig. 3). Because the rise and fall in postprandial glycemia normally occurs over the first 3 h after a meal [Polonsky et al., 1988], the optimal time frame for insulin action is over that same time period. The time to maximal glucose-lowering activity is also reached more quickly with TI than with other inhaled insulins (see below for Exubera[®] and AIR[®]) [Heinemann and Heise, 2004].

Clinical Trial Results

Type 1 diabetes

A 12-week randomized, controlled trial in 110 patients with type 1 diabetes using a basal insulin plus three times daily (TID) prandial insulin regimen found that TI-treated subjects were able to significantly reduce HbA1c levels from baseline (-0.83%), without experiencing weight gain. The control group, which received prandial treatment with an RAA, obtained a similar statistically significant improvement from

baseline in glycemic control (-0.99%). However, the RAA group experienced a weight change of $+0.89$ kg vs. -0.41 kg for the TI group [Boss, 2006].

Type 2 diabetes

- In a 12-week placebo-controlled trial in 123 insulin-naive subjects with type 2 diabetes suboptimally controlled on oral agents, TI significantly reduced mean HbA1c by 0.72%, reduced postprandial glucose levels by $>55\%$ compared with baseline, and reduced maximal glucose levels by $>40\%$. There was not a significant change in weight in this trial; the frequency of hypoglycemia was not different between TI and placebo [Rosenstock et al., 2005a].
- In a dose-titration study in 227 subjects with type 2 diabetes using basal insulin glargine, TI was effective over a wide dose interval and significantly reduced HbA1c and postprandial glucose levels from baseline [Tack et al., 2007]. At the highest dose of 56 TIU per meal (TID), mean HbA1c levels, corrected for baseline HbA1c and basal insulin exposure, were reduced by -0.78% over 11 weeks compared with placebo. Maximal postprandial glucose values were reduced by almost 50% compared with placebo. There was no difference in average insulin glargine dose between TI- and placebo-treated subjects at the end of the trial.
- In a 6-month trial in 309 previously insulin-treated subjects with type 2 diabetes, TI treatment, as an add-on to basal insulin, produced a reduction in HbA1c similar to that of the RAA comparator. Corrected for baseline HbA1c and basal insulin exposure, the change from baseline was -0.90% for TI and -1.10% for the RAA group. There was a significant difference in weight change between the treatment groups, with weight gain experienced in the RAA but not in the TI group. No effect on pulmonary function was observed and the incidence of hypoglycemic events was lower in TI- than in RAA-treated subjects [Boss, 2006].

To date, there have been no clinically meaningful reductions in pulmonary function in TI-treated subjects in completed trials. Ongoing Phase 3 trials are assessing the long-term efficacy and safety of TI in subjects with type 1 and type 2 diabetes.

EXUBERA[®], AERx[®], AND AIR[®] INHALED INSULINS

Exubera[®] is a dry powder short-acting insulin; the delivery system produces an aerosol of insulin, which is then inhaled by the patient. Exubera[®] received FDA approval in 2006, and is the only inhaled

insulin to have reached the market. AERx[®] and AIR[®] are currently in Phase 3 development. AERx[®] insulin Diabetes Management System (iDMS) is an electronic delivery system for inhalation of insulin that uses a battery-powered device with microprocessor-controlled technology to guide patients into the optimal breathing pattern for effective insulin deposition in the lung. The system requires cold storage and is about the size of a paperback book. The AIR[®] inhaler is a small, disposable breath-activated device. The insulin formulation is packaged in capsules that are placed into the inhaler and aerosolized. The patient inhales through the mouthpiece with an inhalation of modest intensity and breath-holding is recommended prior to exhalation. The pharmacodynamic profile of Exubera[®], AERx[®], and AIR[®] are all similar as detailed below.

Absorption

In a study of healthy subjects, the serum insulin t_{\max} for 6 milligrams (mg) of Exubera[®] was 55 min as compared with 148 min for 18 IU of s.c. RHI [Rave et al., 2005]. The maximal serum insulin levels were comparable between the two treatments (66.9 μ U/ml for Exubera[®], 61.0 μ U/ml for s.c. RHI). In a study of healthy subjects, the t_{\max} for 12 U of AIR[®] was 45 min with a C_{\max} of 44 μ U/ml; 12 U of AIR[®] was considered equivalent to 12 U of s.c. insulin lispro [Rave et al., 2007a].

Time-Action Profile

The effectiveness of Exubera[®] vs. s.c. RHI has been assessed with an isoglycemic glucose-clamp study in healthy subjects [Rave et al., 2005]. The time to maximal effect on glucose-lowering (GIR t_{\max}) occurred 143 min after inhalation of 6 mg Exubera[®], and 193 min after injection of 18 IU s.c. RHI. Over the first 180 min post-dose, Exubera[®] delivered less than half of its total glucose-lowering activity. The duration of glucose-lowering activity for Exubera[®] was approximately 6.5 h. The time-action profile for 12 U of AIR[®] was similar, with a time to maximal glucose-lowering activity of 261 min and a broad peak of glucose-lowering activity over more than 6 h [Rave et al., 2007a]. The protracted glucose-lowering activity of AIR[®] may explain the statistically significantly increased rate of nocturnal hypoglycemia observed in patients with type 1 diabetes treated with AIR[®] vs. s.c. insulin lispro [Garg et al., 2006].

Clinical Trial Results

Exubera[®] is clinically effective and provides reductions from baseline in HbA1c that are similar to those achieved by s.c. regular insulin [Skyler et al., 2007]. There are no reports of Exubera[®] in a head-to-head comparison with any other inhaled

insulin, but published pharmacokinetic data for both AIR[®] and AERx[®] are very similar to that of Exubera[®]. The incidence of hypoglycemia is comparable between Exubera[®] and short-acting s.c. insulin in subjects with type 1 diabetes [Skyler et al., 2007], but is greater in Exubera[®]-treated subjects with type 2 diabetes than in those receiving oral antihyperglycemic agents [Barnett et al., 2006a, b; Rosenstock et al., 2005b]. In patients with type 1 diabetes who were treated with Exubera[®] or s.c. insulin for 2 years, the change from baseline in body weight was +0.8 kg for Exubera[®]-treated subjects as compared with +2.0 kg for patients treated with s.c. insulin [Skyler et al., 2007]. A small reduction in lung function relative to treatment with s.c. insulin was observed, occurring within the first few months and stabilizing thereafter [Skyler et al., 2007]. Studies have demonstrated that this effect is reversible over a 3-month discontinuation period.

THE FUTURE OF INHALED INSULIN

Controlling postprandial glycemia is critical to achieving the commonly recognized goals of insulin therapy and diabetes management. The introduction of inhaled insulin early in the course of type 2 diabetes may make prandial supplementation more acceptable to patients and facilitate glycemic control. In a recently published study of subjects with type 2 diabetes who were suboptimally controlled on oral agents, the addition of s.c. prandial insulin aspart provided better glycemic control than the addition of basal insulin detemir, albeit with a greater risk of hypoglycemia and weight gain [Holman et al., 2007]. The risk of hypoglycemia generally increases with improved control and becomes a barrier to reaching glycemic targets. Thus, the development of a prandial insulin with a more physiologic time-action profile should reduce the risk of hypoglycemia and mitigate against weight gain. Delivery via a discreet, handheld device should make prandial administration easier for patients and facilitate full or near normalization of glycemia. In turn, a near-normal level of glycemia will provide concomitant risk reduction for the micro- and macrovascular complications of diabetes.

Postscript

The recent failure of Exubera[®] may be an indication that while needle-free delivery of insulin is attractive, it may not be sufficient to obtain widespread acceptance of prandial therapy [Exubera Official Site, 2007]. In order to meet clinical needs, a more physiologic prandial insulin is required, and the ability to administer it by inhalation through an easy-to-use device will be a further benefit.

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