

The Role of Rapid-Acting Insulin Analogues and Inhaled Insulin in Type 2 Diabetes Mellitus

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ABSTRACT

Background: The availability of rapid-acting insulin analogues and inhaled insulin gives clinicians additional treatment options in the management of patients with diabetes mellitus (DM). Combining rapid-acting insulin analogues with basal insulin can more closely mimic physiologic insulin release to maximize glycemic control.

Objective: The objective of this article was to discuss the role of rapid-acting insulin analogues and inhaled insulin in the treatment of patients with type 2 DM.

Methods: Materials for this article were obtained through an online search of MEDLINE/PubMed and Google (1996–2006) using the search terms *bolus insulin, postprandial, rapid-acting insulin analogues, titration, hypoglycemia, glycemic control, inhaled insulin, and insulins lispro, aspart, and glulisine*.

Results: Glycosylated hemoglobin (A1C) levels and number of all hypoglycemic episodes were similar in patients with type 2 DM taking either mealtime rapid-acting insulin analogues or regular human insulin (RHI). Rapid-acting insulins have been successfully used in basal-bolus regimens with a variety of long- and intermediate-acting insulins, as well as with oral hypoglycemic agents. Injectable rapid-acting insulin analogues markedly decreased postprandial glucose (PPG) levels compared with RHI. Better reduction in PPG levels may be key to achieving target A1C levels in some patients, but long-term outcome studies are needed to assess whether lowering PPG levels decreases cardiovascular risk in patients with type 2 DM. Inhaled insulin may be an option for patients who cannot inject insulin, but route of administration and dosing issues limit its use in many patients. The effect of inhaled insulin on PPG is unclear at this time.

Conclusions: Although rapid-acting insulin analogues are effective in the management of patients with type 2 DM, the limited numbers of studies have yet to demonstrate that these agents have any significant long-term advantage compared with RHI. In addition, they cost more than RHI. Further studies are needed to compare the efficacy of the rapid-acting insulin analogues, to compare the different dosing regimens used with mealtime insulin administration, and to ascertain if the decrease in PPG levels seen with the use of rapid-acting insulin analogues translates into improved glycemic control and perhaps even a reduction in cardiovascular risk in patients with type 2 DM. (*Insulin*. 2007;2:61–67) Copyright © 2007 Excerpta Medica, Inc.

Key words: bolus insulin, type 2 diabetes mellitus, insulin, basal-bolus therapy, inhaled insulin.

INTRODUCTION

The availability of rapid-acting insulin analogues and inhaled insulin gives clinicians additional treatment options in the management of patients with both type 1 and type 2 diabetes mellitus (DM). However, assessing the efficacy of these insulins in patients with type 2 DM is complex because of the variety of treatment regimens and study designs involving rapid-acting insulins.

Ideal insulin replacement therapy should mimic physiologic insulin release.¹ It should thus include a basal component of low-level constant release that affects fat and hepatic glucose metabolism, plus a proportional prandial response to glucose intake.¹ The pharmacodynamic and pharmacokinetic (PK) properties of previously available insulins, such as neutral protamine Hagedorn (NPH) and regular human insulin (RHI), make them less-than-ideal replacements. Slow

absorption of RHI provides a peak effect and response that is later and less physiologic.¹ Intermediate- and long-acting insulins, with their large variation in absorption and activity in individual patients, can make it challenging for even the most conscientious patients to maintain tight control of blood glucose (BG) level. The rapid-acting insulin analogues, however, allow providers and patients to more closely achieve normal physiologic insulin-response patterns. The activity of long-acting insulin analogues (ie, insulin glargine) closely mimics normal basal-insulin release.¹ The rapid-acting insulin analogues (ie, insulins lispro, aspart, and glulisine) more closely follow normal physiologic prandial-insulin response compared with RHI.¹⁻⁵

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The objective of this article was to discuss the role of rapid-acting insulin analogues and inhaled insulin in the treatment of patients with type 2 DM.

MATERIALS AND METHODS

Materials for this article were obtained through an online search of MEDLINE/PubMed and Google (1996–2006) using the search terms *bolus insulin, postprandial, rapid-acting insulin analogues, titration, hypoglycemia, glycemic control, inhaled insulin, and insulins lispro, aspart, and glulisine.*

RAPID-ACTING INSULIN ANALOGUES (BOLUS INSULINS)

The 3 injectable rapid-acting insulin analogues (ie, insulins lispro, aspart, and glulisine) have similar PK properties (Table I).¹⁻⁵ In general, all 3 analogues reach twice the maxi-

mum concentration in half the time as do equivalent doses of RHI.² Insulin analogues achieve higher concentrations and more rapid peak levels compared with RHI because RHI has a strong affinity for self-association, and insulin dimers and monomers form larger hexamers (6 closely bound molecules). Hexamers diffuse more slowly than dimers and monomers into the bloodstream, thereby delaying RHI onset and peak activity.¹

All injectable insulins come in a standardized concentration of 100 U/mL. Insulin analogues are available in 10-mL vials and 3-mL cartridges for use in an insulin pen system, and all are approved for use in insulin pump systems. Only NPH can be mixed with the rapid-acting insulin analogues, and the mixture must be used immediately.

The insulin analogues are less stable than RHI and expire after 28 days once opened. Insulin glulisine must be stored at <77.0°F; insulins aspart and lispro at <86.0°F. Based on the average number of units per day a patient uses, much of an injectable insulin analogue will go to waste. If patients use insulin analogues after the expiration date, they may experience suboptimal efficacy and temporary loss of BG control. However, a patient who takes 20 U/d will have a 50-day supply of insulin and may be tempted to use expired insulin for 22 days more to save money rather than waste ~50% of the vial. All the injectable rapid-acting insulins cost >2 times as much as RHI, and the insulin pen systems cost 35% more per unit of insulin than the same insulin in a 10-mL vial (Table I).

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All the insulin analogues have shown efficacy in patients with type 2 DM.^{6,7} One review and meta-analysis found that

Table I. Pharmacokinetic properties and costs of rapid-acting insulin analogues.¹⁻⁵

Insulin Preparation	Onset of Action, min	Peak Action	Duration of Action, h	Price per 10-mL Vial, \$*	Price per mL per Pen, \$
Regular human insulin	30–60	2–3 h	8–10	35.00	NA
Insulin lispro (Humalog®)†	10–30	30–90 min	3–6	78.00	10.00
Insulin aspart (NovoLog®)‡	10–20	30–90 min	3–5	81.00	9.63
Insulin glulisine (Apidra®)§	10–15	30–90 min	3–5	79.00	10.49
Inhaled insulin (Exubera®)¶	10–20	30–90 min	6	Not available	NA

NA = not applicable.

*Prices available at: <http://www.drugstore.com>. Accessed November 19, 2006.

†Eli Lilly and Company, Indianapolis, Indiana.

‡Novo Nordisk A/S, Princeton, New Jersey.

§sanofi-aventis, Bridgewater, New Jersey.

¶Pfizer Inc., New York, New York.

the rapid-acting insulin analogues had only minor or no benefit in metabolic control and hypoglycemia compared with RHI.⁸

INHALED INSULIN COMPARED WITH INJECTABLE RAPID-ACTING INSULIN ANALOGUES

Injectable rapid-acting insulin analogues differ from RHI primarily in their PK properties. The first inhaled insulin, insulin human [rDNA origin] inhalation powder (Exubera®; Pfizer Inc., New York, New York), differs from injectable insulin analogues and RHI in several ways. It is formulated as a dry powder of RHI that patients inhale to take advantage of the lungs' large vascular bed and alveolar permeability to deliver the insulin directly into the bloodstream.⁹ Inhaled insulin administration is recommended 10 minutes before mealtime.⁹

Table I compares the PK properties of the rapid-acting insulin analogues and inhaled insulin. Unlike injectable insulins, which are dosed in units, inhaled insulin is dosed in milligrams and is available in manufactured blister packages. The 1-mg blister package delivers insulin equivalent to ~3 U of SC RHI, while the 3-mg blister package is equivalent to ~8 U. Confusion exists because 3 consecutive inhalations of a 1-mg blister package yield more insulin than a single inhalation of a 3-mg blister package. The manufacturer recommends substituting two 1-mg blister packages for a 3-mg blister package if a patient lacks 3-mg blister packages.¹⁰

This lack of equivalence is problematic when patients or providers make small dosing adjustments based on SC insulin equivalents. Patients or providers may easily miscalculate the combination of blister packages to use, resulting in less-than-optimal control. Dosing calculations when initiating therapy with inhaled insulin can be done via manufacturer-provided tables or guidelines for dosing by body weight or by conversion of current SC insulin dose. Dosing issues will require intensive educational efforts and careful monitoring of plasma glucose to ensure appropriate use.¹⁰

Dosing issues related to inhaled insulin will require intensive educational efforts and careful monitoring of plasma glucose to ensure appropriate use.

Clinical trials with inhaled insulin excluded patients who had a body mass index >35 kg/m² or used >150 U/d of insulin and limited maximum inhaled insulin doses to the equivalent of 16 U of SC insulin per meal.⁹⁻¹² Therefore, given the limited choice in blister packaging, inhaled insulin is not a practical treatment option for patients with type 2 DM who display a large component of insulin resistance and require large doses of prandial insulin to achieve tight BG control. For example, a patient requiring 65 U of insulin with each meal would have to inhale seven 3-mg blister packs and three 1-mg blister packs to achieve that dose.

In addition, compared with the rapid-acting insulin analogues, inhaled insulin has an expanded adverse-event profile and more limited applicability due to its route of administration. Inhaled insulin is not recommended for patients with impaired lung function, chronic obstructive pulmonary disease, or asthma; for patients with a forced expiratory volume in 1 second (FEV₁) or a carbon monoxide-diffusing capacity of <70% predicted value; or for patients who have other conditions or take medications that might affect the alveoli or the lung vascular bed.¹⁰

Patients who are currently smoking or stopped smoking <6 months ago should not use inhaled insulin because smoking increases insulin absorption.¹⁰ Similarly, bronchodilators such as albuterol, given 30 minutes before an inhaled insulin dose, could increase the peak concentration of insulin by ≤50%.¹⁰ Spirometry is recommended in all patients before initiation of therapy to screen for pulmonary dysfunction and establish baseline pulmonary function. Because patients who use inhaled insulin show a small but nonprogressive decline in pulmonary function, spirometry should be repeated 6 months after initiation of therapy and annually thereafter.¹⁰ Data addressing pulmonary changes in patients using inhaled insulin for >2 years are not yet available, but in patients who discontinued inhaled insulin after 2 years, the FEV₁ normalized after 6 weeks.¹⁰

In addition to hypoglycemia, inhaled insulin's primary adverse effects are associated with its route of administration. Cough occurred in 10% to 20% of patients within seconds to minutes after inhalation.¹⁰ Although the cough was mostly mild and nonproductive, 1.2% of patients discontinued inhaled insulin due to cough.¹⁰ Xerostoma, otitis media, and nonspecific chest pain occurred in 1% to 3% of patients. Other respiratory adverse effects such as dyspnea and pharyngitis were uncommon, occurring in <0.5% of patients.¹⁰

The literature is unclear regarding the impact of inhaled insulin on postprandial glucose (PPG) levels. One study¹² showed significant reductions ($P < 0.001$), but 2 others showed little or no change.^{9,11}

RAPID-ACTING INSULIN ANALOGUES, REGULAR HUMAN INSULIN, POSTPRANDIAL BLOOD GLUCOSE LEVELS, AND HYPOGLYCEMIA

All the rapid-acting insulin analogues are administered 3 times a day at mealtimes, either alone or as part of a basal-bolus regimen.¹⁻⁸ The rapid-acting analogues are also used at mealtimes 2 or 3 times a day as a mixture with intermediate-acting analogues such as insulin lispro 75/25 (Humalog® Mix75/25™; Eli Lilly and Company, Indianapolis, Indiana).¹³ Many of the studies involving rapid-acting insulin analogues primarily compare them with RHI and focus on the relative effect on PPG levels and the incidence of hypoglycemia. Multiple studies demonstrate that use of appropriately dosed mealtime, or preprandial, rapid-acting insulin results in a 20% to 50% lower peak PPG level than use of RHI 30 to 45 minutes before a meal.^{1,2,14} In addition, several studies have reported a lower incidence of hypo-

glycemia, especially nocturnal, in patients receiving rapid-acting insulin analogues compared with those receiving RHI.^{15,16} However, other studies found no or nonsignificant differences in the rate of hypoglycemia.^{8,17,18}

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Over the last several years there has been renewed interest in the impact of PPG on glycosylated hemoglobin (A1C) and on the macrovascular complications of DM.^{19,20} Rapid-acting insulin analogues (ie, insulins lispro, aspart, and glulisine) have a greater impact on PPG than does RHI, and this finding has further stimulated research into the effect of rapid-acting insulins on PPG. Although the clinical contribution of PPG to A1C levels varies with the level of disease control, attention to PPG levels may help patients with relatively good control of their type 2 DM reach target A1C levels sooner and more often.²⁰ Similarly, there is increasing evidence that controlling or lowering PPG levels with rapid-acting insulins reduces surrogate atherosclerotic markers (eg, endothelial dysfunction) and might theoretically lead to reduced cardiovascular risk.^{19,20} However, at this time, no

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large studies show long-term positive cardiovascular outcomes from lowering PPG levels.

PRACTICAL USE OF RAPID-ACTING INSULINS

Most published studies focused on comparing the impact RHI and rapid-acting insulin analogues have on PPG levels and hypoglycemia, and important details regarding the specific dosing or titration requirements of these insulins were sometimes omitted from the Methods sections. This makes the analysis of clinical trials for practical application problematic. Among the details omitted were methods of dosage titration,^{2,6,7,16,21} PPG target levels,^{6,7,14,15} the presence or absence of dosing based on carbohydrate counting,^{2,6,7,16,17,21} details on dietary restrictions,^{2,6,7,17,22} and the exact timing of insulin administration.^{2,6,7,14,15}

Rapid-acting insulins have been studied primarily as mealtime regimens alone^{2,12,14,23} (Table II) or in modified basal-bolus regimens combined with oral antidiabetic drugs, NPH insulin, and insulins glargine or detemir as the basal hypoglycemic agent (Table III).^{6,9-12,16-18,21,22,24} Rapid-acting dosage regimens, if fully described, included fixed dose based on weight^{9,23} and dosage titration based on 1- to 2-hour PPG,^{7,9,17,18} A1C,^{2,12,16} preprandial plasma glucose,^{2,6,7,11,12,16,18,21} or fasting plasma glucose^{12,15} level either alone or in some combination. In many studies, PPG levels were lower in patients who used rapid-acting insulin analogues than in those using RHI.^{2,12,14,17,18} However, rapid-acting insulin analogues and RHI had a similar impact on A1C in most studies when reported.^{6,8,9,11,16-18}

In the published studies, administration times for rapid-acting insulin analogues relative to meals ranged from 15 minutes before mealtime to 20 minutes after the meal began. The most frequent time for administration was immediately before

Table II. Studies of rapid-acting insulin monotherapy in patients with type 2 diabetes mellitus.

Reference	Study Design	No. of Patients	Regimen	Primary End Point	Results
Anderson et al ²	Randomized, open-label, crossover	722	Insulin lispro vs RHI	PPG level	PPG level 53% lower; less hypoglycemia at 2 h
Rosenstock et al ¹²	Randomized, controlled, open-label, 12 wk	102	INHI	A1C level	-1.4% vs OHA; A1C level <7.0% in 16.7% vs 1% taking OHA
Perriello et al ¹⁴	Randomized, double-blind, crossover	27	Insulin aspart vs RHI	PPG level	20% lower PPG level vs RHI
DeFronzo et al ²³	Randomized	143	INHI vs rosiglitazone 8 mg	A1C level	A1C level <7.0% in 44.7% vs 18% taking rosiglitazone

RHI = regular human insulin; PPG = postprandial glucose; INHI = inhaled human insulin; A1C = glycosylated hemoglobin; OHA = oral hypoglycemic agent.

a meal. Cases of early hypoglycemia were reported in patients who switched from RHI to a rapid-acting insulin analogue on a unit-for-unit basis.^{21,25} The authors of one brief report recommended that rather than replacing RHI on a unit-for-unit basis, a lower dose of the rapid-acting insulin analogue should be used to avoid hypoglycemia.²⁵ There are currently no published studies in which patients with type 2 DM base their bolus rapid-acting insulin doses on the amount of carbohydrates consumed, which is a popular approach for patients with type 1 DM; further research of this option is therefore indicated.

DISCUSSION AND CONCLUSIONS

Rapid-acting insulin analogues are effective in the management of patients with type 2 DM. Their availability gives clinicians additional treatment options, and combining rapid-acting insulin analogues with basal insulin can more

closely mimic physiologic insulin release to maximize glycemic control. However, studies are limited and have yet to demonstrate that rapid-acting insulin analogues have a demonstrable long-term advantage compared with RHI. In addition, the rapid-acting insulin analogues cost 2 to 3 times more than RHI,²⁶ which may limit their use in many patients. As for inhaled insulin, it may improve disease control in patients who require insulin but refuse to inject it. However, dosing issues will limit the number of patients able to use inhaled insulin.

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Table III. Studies with rapid-acting insulin analogues in basal-bolus regimens in patients with type 2 diabetes mellitus (DM).

Reference	Study Design	No. of Patients	Regimen	Primary End Point	Results
Radermecker and Scheen ⁶	Randomized, controlled	107	CSII lispro vs insulin lispro/glargine	A1C level	No difference in A1C level
Hollander et al ⁹	Randomized, open label	309	INHI/ultralente vs RHI/NPH twice daily	A1C level	-0.7% with INHI/ultralente; -0.6% with RHI/NPH; -9.41 mg/dL PPG level with INHI vs RHI/NPH
Cefalu et al ¹¹	Randomized, open label	26	INHI/ultralente vs usual insulin therapy	A1C level	-0.7%; no difference in PPG level
Raslova et al ¹⁶	Randomized, open label	394	Insulin aspart/detemir vs NPH basal/RHI bolus	A1C level	No difference in A1C level; -0.65% vs -0.58% and less weight gain with insulin aspart/detemir
Dailey et al ¹⁷	Randomized, open label	1186	Basal NPH twice daily; bolus RHI vs preprandial insulin glulisine (breakfast and dinner)	A1C level	-0.11% with insulin glulisine vs RHI
Anderson et al ¹⁸	Randomized, open label	295 (type 2 DM) 336 (type 1 DM)	Basal NPH or ultralente bolus RHI vs insulin lispro	A1C level	No difference in A1C level or hypoglycemia
Bastyr et al ²¹	Randomized, open label	423	Insulin lispro + sulfonylurea vs insulin lispro + NPH or NPH + sulfonylurea	A1C level	-1.6% with insulin lispro + sulfonylurea; -1.45% with insulin lispro + NPH; -1.17% with NPH + sulfonylurea
Poulsen et al ²²	Randomized, open label	16	NPH/RHI mix (control) vs metformin, rosiglitazone, and preprandial insulin aspart	A1C level	-2.0% with metformin, rosiglitazone, and preprandial insulin aspart vs control
Weiss et al ²⁴	Randomized, open label	68	OHA (control) vs OHA + INHI	A1C level	-2.3% with OHA + INHI vs control

CSII = continuous subcutaneous insulin infusion; A1C = glycosylated hemoglobin; INHI = inhaled human insulin; RHI = regular human insulin; NPH = neutral protamine Hagedorn; PPG = postprandial glucose; OHA = oral hypoglycemic agent.

When used as mealtime doses, rapid-acting insulin analogues are effective alone, in a variety of basal-bolus regimens, or as mixtures with intermediate-acting insulin analogues in patients with type 2 DM. When given 30 minutes before mealtime, they are all superior to RHI in lowering PPG levels. However, the decrease in PPG levels has not translated into decreased A1C levels compared with RHI. Until long-term outcome studies establish that decreasing PPG levels reduce cardiovascular complications in patients with type 2 DM, there is no compelling reason to choose rapid-acting insulin analogues over RHI. The Cochrane Metabolic and Endocrine Disorders Group, in their 2006 review comparing the new insulin analogues with RHI, concluded: "Our analysis suggests only a minor benefit of

short acting insulin analogues in the majority of diabetic patients treated with insulin. Until long-term efficacy and safety data are available, we suggest a cautious response to the vigorous promotion of insulin analogues."²⁷ Given the limited data on inhaled insulin available at this time, this group's recommendations should also apply to inhaled insulin.

Further studies are needed to compare the efficacy of the rapid-acting insulin analogues, to compare the different dosing regimens used with mealtime insulin administration, and to ascertain if the decrease in PPG levels seen with the use of rapid-acting insulin analogues translates into improved glycemic control and perhaps even a reduction in cardiovascular risk in patients with type 2 DM.

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