Inhaled Insulin: A Breath of Fresh Air? A Review of Inhaled Insulin

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ABSTRACT

Purpose: Despite many advances in diabetes care over the last century, some elements of insulin therapy remain inadequate for optimal care of the patient with diabetes. There is a need for improved pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues to mimic physiologic insulin secretion. In addition, a major barrier to successful insulin therapy has been patient resistance. Alternative routes of insulin administration, including inhaled insulin, have been under investigation for several years. This review discusses the rationale for pulmonary delivery of insulin, compares previous inhaled insulin products, reviews the literature on the safety and efficacy of a current inhaled insulin formulation under investigation, and compares this product with other prandial insulin products.

Methods: English-language studies and reviews of inhaled insulin were searched in MEDLINE, the ClinicalTrials.gov registry (through May 2014), and the US Food and Drug Administration Website.

Findings: Inhaled insulin has several favorable characteristics due to pulmonary anatomy/physiology and the lack of injections. Pharmacokinetic and pharmacodynamic studies have shown a time–action profile suitable for prandial insulin use. Inhaled insulin seems to be safe and effective compared with other prandial insulin products and may be preferable to subcutaneous rapid-acting insulin analogues in terms of time–action profiles and rates of hypoglycemia. Small decreases in forced expiratory volume in 1 second (FEV1) have been shown with inhaled insulin, although this finding is not progressive over time and reverses with cessation of the medication.

Implications: Although several inhaled insulin products have been under investigation, only one (Exubera® [Nektar Therapeutics, San Carlos, California/Pfizer Inc, New York, New York]) was approved by the US Food and Drug Administration, and it was pulled from the market after only a short period of time. Technosphere® insulin (MannKind Corporation, Valencia, California) is currently the only inhaled insulin that remains under investigation. A review of the past and present literature on inhaled insulin is pertinent in understanding the current status of inhaled insulin and its risks and benefits. The current literature suggests that inhaled insulin could be a valuable option for prandial insulin administration, with a favorable risk to benefit ratio in some patients. (*Clin Ther.* 2014;36:1275–1289) © 2014 Elsevier HS Journals, Inc. All rights reserved.

Key words: diabetes, glycemic control, inhalation, inhaled, insulin, pulmonary.

INTRODUCTION

Improvements in subcutaneous insulin have allowed for more physiologic regimens since its discovery in the 1920s. The development of rapid-acting insulin analogues has improved pharmacokinetic and pharmacodynamic properties of insulin formulations. However, these formulations continue to fall short of physiologic needs to control postprandial hyperglycemia, with delayed onset of action and prolonged effects leading to excessive hyperglycemia after eating and delayed hypoglycemia.[1] The importance of tight glycemic control has been shown to prevent and/or delay long-term complications of diabetes.[2] The success of insulin therapy, however, depends on its physiologic properties as well as on its proper use. Barriers to patient use of subcutaneous insulin include anticipated pain, anxiety, inconvenience, fear of hypoglycemia, and concern about weight gain.[3] Evidence suggests that patients may be reluctant to start insulin when prescribed or to delay starting treatment.[4] In one study of patients with

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type 2 diabetes (T2DM), 28% of subjects reported they were unwilling to start insulin, 45% reported resistance to insulin therapy due to restrictions on daily life (eg, harder to travel, eat out), and 43% of patients reported fear of hypoglycemia.[5] Practical issues can also occur (eg, lipodystrophy, lipohypertrophy) from several years of recurrent injections.

It has been >90 years since the first therapeutic use of insulin by Banting and Best. Since that time, researchers have been searching for alternate modes of insulin delivery, including transdermal, ocular, oral, buccal, nasal, rectal, vaginal, and uterine delivery systems. Reports of pulmonary delivery of aerosolized insulin was first shown in the 1920s to decrease blood glucose levels.[6] However, these methods have historically failed as insulin delivery systems, primarily due to low bioavailability. For example, oral bioavailability of insulin is limited due to extensive enzymatic and chemical degradation in the gastrointestinal tract and inability to cross intestinal mucosa due to the large hydrophilic nature.[7,8] Currently, several alternative methods of delivery are under investigation. Potential improvements include improved absorption of transdermal insulin-using iontophoresis (electrical currents), low-frequency ultrasound, and transfersomes (lipid vesicles) and increasing bioavailability of oral insulin such as stabilizing degradation and using microspheres to enhance absorption. The use of buccal insulin has also been proposed to overcome some of the aforementioned issues with oral insulin.[9]

Therefore, there is a need not only for alternative modes of insulin delivery but for a more physiologic, rapid-on/rapid-off, prandial insulin to improve glycemic control and reduce hypoglycemia. The present review focuses on the past and present data regarding the safety and effectiveness of inhaled insulin products as prandial insulin.

MATERIALS AND METHODS

A systematic search was conducted in MEDLINE and the ClinicalTrials.gov registry (through May 2014) to find English-language studies and review articles of prior and current inhaled insulin products. The following search terms were used: *diabetes, glycemic control, inhaled, inhalation, insulin, pulmonary, Exubera®,* and *Technosphere® insulin*. We searched for additional publications in citation sections of the recovered articles. The US Food and Drug Administration (FDA) Website was also reviewed to find briefing documents on Exubera® (Nektar Therapeutics [San Carlos, California]/Pfizer Inc [New York, New York]) and Afrezza® (MannKind Corporation, Valencia, California).

RESULTS

Pulmonary Delivery of Insulin

Of the alternative modes of delivery investigated thus far, pulmonary delivery of insulin has shown the most promise, perhaps due to advantageous characteristics for medication delivery. Pulmonary delivery of insulin has been shown to have a ~4- to 40-fold increase in bioavailability compared with nasal, rectal, buccal, and conjunctival formulations.[10] The lung is highly vascularized with ~500 million alveoli, providing an extremely large surface area (50–140 m^2).[7] The thin alveolar-capillary barrier (0.2 μm) allows for rapid onset of action, although the exact mechanism of absorption is unknown.[7,11] The lung also lacks certain peptidases found in the gastrointestinal tract that can break down insulin before it is used systemically.[7] Although much knowledge has been gained about pulmonary delivery of medications by the use of asthma medications, these delivery systems are not suitable for insulin administration. Unlike with asthma medications, delivery of insulin requires precise and consistent dose delivery deep into the lungs where it is needed for rapid absorption.[3,9] Several studies and historical insulin delivery systems have revealed additional limitations, including particle size and velocity, drug deposition and clearance, device complexity, patient compliance, and concomitant disease.[9] Particle size may be one of the most important factors in delivering insulin to the deep lung. Enhanced absorption is seen with a particle size between 1 and 3 μm in diameter because larger particles are exhaled and particles >5 μm are deposited in the upper airways or swallowed.[11,12] In addition, effectiveness of inhaled insulin varies with respiratory factors, including inspiratory effort, tidal volume, and peak flow.[13,14]

Inhaled Insulins: A Historical Perspective

Evaluation of historical inhaled insulin is helpful in understanding the current market. Several inhaled insulin delivery systems have been in development, most notably Exubera, AERx® Insulin Diabetes Management System (iDMS) (Aradigm Corporation

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