DOI: 10.7860/JCDR/2017/23626.9732

Review Article

Internal Medicine Section

Inhaled Insulin - Current Direction of Insulin Research

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ABSTRACT

Diabetes Mellitus (DM) is a metabolic disorder characterized by relative or absolute deficiency of insulin, resulting in hyperglycemia. Subcutaneous insulin and Oral Hypoglycaemic Agents (OHA) constitute the main treatment option for DM. Insulin is administered by injection or continuous infusion to control glucose levels mainly in Type I diabetes. Newer routes both oral and non oral, for insulin administration are current direction of insulin research as insulin injection therapy is burdensome and painful for many patients. Inhalational insulin is an attractive alternative for systemic administration of insulin given its accessibility and large alveolar-capillary network of lungs for drug absorption. Afrezza, inhaled insulin has been recently approved by Food and Drug Administration (FDA). It is a new, quicker acting inhalable insulin with a different and safer pharmacokinetic profile in comparison to previously failed inhaled form of insulin.

Keywords: Afrezza, Diabetes, Exubera

INTRODUCTION

According to WHO, latest 2016 data shows global prevalence of DM has reached an astounding figure of 422 million [1]. While staggering, these numbers fall short of conveying the full magnitude of the problem. Impact of DM includes disabling complications, economic burden and increase in disability adjusted life years. Though seems challenging to implement, optimal management of DM has shown to decrease the associated complications.

Insulin now-a-days is a treatment option for both Type I and Type II diabetes. For patients with Type II DM whose blood sugar is not maintained with lifestyle intervention or with OHA, insulin therapy must be added. The United Kingdom Prospective Diabetes Study (UKPDS) showed that to keep Type II diabetes under control (HbA1c<7%); insulin was needed within six year for approximately 50% people with diabetes [2]. Use of insulin requires injection for delivery either via syringe or Continuous Subcutaneous Insulin Infusion (CSII) via insulin pump, as oral administration results in loss of biopotency, owing to the breakdown in stomach. Non oral route specifically, the lungs provide an attractive alternative for systemic administration of therapeutic polypeptide including insulin. The large surface area, good vascularization, immense capacity for solute exchange and ultra-thinness of the alveolar epithelium facilitates systemic delivery of insulin via pulmonary administration given its accessibility and large alveolar-capillary network for drug absorption. Amongst the different advances in insulin therapy, a number of clinical trials have demonstrated proof of principle for pulmonary delivery of insulin for diabetics.

Inhalable Insulin/Inhaled Insulin is insulin in powdered form delivered to the lungs with an inhaler. It is considered as paradigm shift in insulin delivery, as it differs in route of administration, dosing units, patient eligibility and required testing for safety in a periodic interval. In 2007, a review on inhaled insulin concluded that though it appears to be equally effective, but not superior to injected insulin. It is also unlikely to be cost effective owing to much more additional cost. The additional cost is so much more that it is unlikely to be cost-effective [3].

Exubera, an inhaled form of rapid acting insulin developed by Pfizer, became the first inhaled insulin product to be marketed in 2006 [4], but poor sales led Pfizer to withdraw it in 2007 [5]. Currently Afrezza developed by Mannkind, that uses a different technology (technosphere) was approved by the FDA in 2014 [6].

History

In 1921, Insulin was introduced by Banting and Best from the University of Toronto as an injectable agent. Insulin from animal source like beef insulin was the first commercially available preparation followed by porcine insulin. Later human insulin (humulin) was synthesized by recombinant DNA technology. In 1924, idea of inhalable insulin was first introduced by German researchers [7]. Years of failure lead to pavement of new ideas that used new technologies to turn insulin into a concentrated powder with particles size suitable for inhalation.

In the 1980s Nektar Therapeutics developed technology to convert insulin into small particles later they licensed to Pfizer. After development of concrete methods, human tests began in the late 1990s [7]. In 2006 FDA first approved the use of Exubera, by Pfizer [4]. It was approved in the UK in August 2006, but was used only for people who had problems with needles [8]. However, in 2007, Exubera failed to gain acceptance among patients and physicians.

In June, 2014, the FDA approved Affreza for both Type I and Type II adult diabetics, with a label restriction for patients having asthma, active lung cancer or Chronic Obstructive Pulmonary Disease (COPD) [6].

Inhaled as Alternative to Conventional Insulin

- In one study, Inhaled insulin successfully managed subcutaneous insulin resistance syndrome (rare condition due to rapid degradation of insulin in subcutaneous tissue) [9].
- Literature showed glycemic control as assessed by mean decrease in HbA1c from base line to end point was comparable between the inhaled and conventional treatment group [10].
- The frequency and nature of adverse events reported with inhaled insulin appear to be comparable to subcutaneous insulin, with the exception of cough though it decreases in incidence and prevalence with continued use.

Why Exubera Failed?

To achieve a therapeutic response, in comparison to subcutaneous route, higher dose of inhaled insulin is required due to inefficient absorption. Administration of Exubera involved the use of a bulky device to dispense powdered human insulin with little dosing flexibility [5].

Afrezza: Pros and Cons

Pros:

It is a drug-device combination product which is rapid acting inhaled insulin, administered at the beginning of each meal.

Drug's safety and effectiveness were evaluated in both Type-I and II diabetes patients (Total 3,017 participants) [11].

It uses a different inhaled insulin formulation (2.5μm) and technosphere technology, which appears to have a more convenient delivery system and greater dosing flexibility.

What is Technosphere technology?

It contains recombinant human insulin dissolved with powder (fumaryl diketopiperazine). Once inhaled, technosphere insulin is rapidly absorbed upon contact with lung surface [12]. Inhalable insulin is delivered with a thumb size inhaler with a rather increased dosing flexibility [13]. Both components, insulin and powder (fumaryl diketopiperazine) are almost completely cleared from the lungs of healthy individuals within 12 hours of inhalation. In contrast to Exubera (8-9%) only 0.3% of insulin of inhaled insulin remained in lungs after 12 hours [14].

Cons:

May develop an increase in serum antibody levels though not related to any significant clinical change.

Acute bronchospasm in patients with asthma and COPD. May cause hypoglycemia, cough and throat pain/irritation.

Significant decrease in Diffusing Capacity of Lungs for Carbon Monoxide (DLCO) relative to subcutaneous insulin.

Smoking appears to enhance insulin absorption [15].

*FDA approved Afrezza with a caution (Risk Evaluation and Mitigation Strategy) for a communication plan to inform health care professionals about the serious risk of acute bronchospasm associated with Afrezza [15].

CONCLUSION

- It is not a substitute for long acting insulin.
- It must be used in combination with long acting insulin in Type I diabetes.
- Not recommended for treatment of Diabetic Ketoacidosis (DKA) or in patient who smoke.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Sep 08, 2016**
Date of Peer Review: **Nov 28, 2016**
Date of Acceptance: **Jan 06, 2017**
Date of Publishing: **Apr 01, 2017**