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INHALABLE INSULIN: A REVOLUTION IN DIABETES MANAGEMENT

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Abstract - Considerable time and financial resources have been dedicated to the development of new medications that target various essential enzymes and signaling pathways, which have temporarily aided in mitigating this growing pandemic. Insulin continues to be regarded as the gold standard for treatment; however, it is frequently rejected by both patients and healthcare professionals (clinical inertia) due to the method of administration of this medication. Although ultra-short-acting insulin analogues assist in managing prandial glucose spikes, they necessitate 2-3 doses depending on meal intake. Furthermore, long-acting basal insulin is often needed to replicate normal physiological insulin baseline levels. This results in an average of 2-4 insulin injections per day, which many individuals find quite distressing. Patients frequently feel overwhelmed by the necessity of finger pricks for regular blood glucose monitoring, and the prospect of tracking blood glucose levels has often deterred a significant number of patients who guess their sugar levels before and after meals. Insulin therapy requires more stringent blood glucose monitoring, and in cases of hypoglycemic episodes or uncontrolled hyperglycemias, multiple finger pricks may be necessary. The discrepancies in blood glucose readings across various Point of Care (POC) glucometer devices do not alleviate the situation and only contribute to the existing frustration. Emphasizing alternative and innovative drug delivery methods for existing molecules can help shift the therapeutic paradigm towards more favorable outcomes. This article will explore one such transformative change in the drug delivery of insulin.

Keywords: Inhaled Insulin; Exubera, Afrezza; Hba1c Reduction; Postprandial Blood Glucose

1. INTRODUCTION

According to the National Diabetes Statistics Report, 29.1 million people have diabetes mellitus (DM) in the U.S., or approximately 9.3% of the population. DM imposes a financial burden on both patients and the health care economy, with direct and indirect costs totaling $245 billion in 2012.[1]All patients with type-1 DM (T1DM) require insulin therapy. Patients with type-2 DM (T2DM) may also become dependent on exogenous insulin as their disease progresses. Approximately 6 million people in the U.S. require insulin therapy. Insulin therapy allows for better glycemic control, but patients are often hesitant to make the transition to insulin because of its adverse-event profile (e.g., hypoglycemia, weight gain) and because of fear of injections. Since injectable insulin was introduced into clinical practice in 1922, other routes of administration have been explored. Inhaled insulin, for example, offers the advantage of a larger area of absorption—approximately 70 to 140 square meters, or half of a tennis court. In 1924, the first study of inhaled insulin was conducted in human subjects at doses 30 times higher than that of the subcutaneous (SC) route of administration. In 2006, the Food and Drug Administration (FDA) approved the first inhaled insulin for patients with T1DM or T2DM. Exubera (Nektar Therapeutics/Pfizer) was derived from recombinant human insulin (rDNA origin), with a bioavailability of approximately 60%. It was available as a spray-dried insulin powder packaged in blisters containing 1 mg or 3 mg of insulin. Despite the promise of a new delivery system, Exubera did not find a profitable niche in the insulin market. Twenty-one months after its approval, the product was voluntarily withdrawn from the market because of low sales. The failure of Exubera may have resulted from several factors, including the high cost of the inhaler; dosing in milligrams, which may have confused patients who had been receiving conventional insulin therapy that was measured in units; the large size of the device; and an FDA warning regarding the potential for primary lung cancer.

Novel strategies for the administration of inhaled insulin continued to be investigated, and in July 2014 the FDA approved Afrezza (insulin human) inhalation powder (MannKind Corp./Sanofi-Aventis US) for patients with T1DM and T2DM. Afrezza employs the new Gen2 inhaler (Figure 1), which is smaller and easier to use than the previously available Exubera device.

The first two rapid-acting inhaled insulins on the market—Exubera in 2006 and Afrezza in 2014—represented yet another innovation milestone. In theory, inhaled insulin eliminated the psychological barriers associated with subcutaneous insulin delivery, such as needle phobia and incorrect injection technique. However, in October 2007, Pfizer withdrew Exubera from the market, and in January 2016, Sanofi withdrew from a $925 million marketing agreement with MannKind for Afrezza; both removals were due to poor sales volume. Although patients and providers have been searching

for years for alternatives to injecting insulin, Exubera has already failed, and Afrezza's destiny is uncertain.

CASE STUDY

IN 2006, Exubera was the first inhaled insulin approved by the U.S. Food and Drug Administration (FDA). It showed noninferiority in efficacy with regard to A1C lowering in both type 1 diabetes and type 2 diabetes compared to mixed regular/NPH insulin. Exubera was indicated as combination therapy in patients with type 1 diabetes, to be used in conjunction with a longer-acting insulin . In patients with type 2 diabetes, Exubera could be used either as monotherapy or in combination with a longer-acting insulin or oral antidiabetic agents.

Contraindications included smokers and patients who had stopped smoking within the past 6 months. Because of an increased risk of hypoglycemia with smoking, patients who resumed smoking while on Exubera were advised to immediately discontinue using the product. Because of changes in pulmonary lung function affecting absorption of the drug and potentially leading to increased hypo- or hyperglycemia risk, Exubera was also contraindicated in patients with unstable or poorly controlled lung disease such as asthma or chronic obstructive pulmonary disease.

With subcutaneous insulin administration, lipohypertrophy is one complication that can affect patients. The cause is likely multifactorial and could involve poor injection site rotation or poor injection technique, but also the growth factor properties of insulin. During clinical trials of Afrezza, there were two cases of lung cancer during 2,750 patient-years of exposure. Both cases occurred in smokers exposed to Afrezza; no subjects in the placebo cohorts were diagnosed with lung cancer. After clinical trial completion, the investigators reported that two nonsmokers also were diagnosed with the same type of cancer (squamous cell lung carcinoma). Could the growth factor properties of insulin that may be implicated in lipohypertrophy when insulin is administered subcutaneously be the cause of pulmonary malignancy when it is inhaled? Although animal carcinogenicity studies indicate an absence of neoplasias and preneoplastic signals in Afrezza-treated rats, there are not yet enough human data to confidently confirm or dismiss the risk of pulmonary malignancy with inhaled insulin.

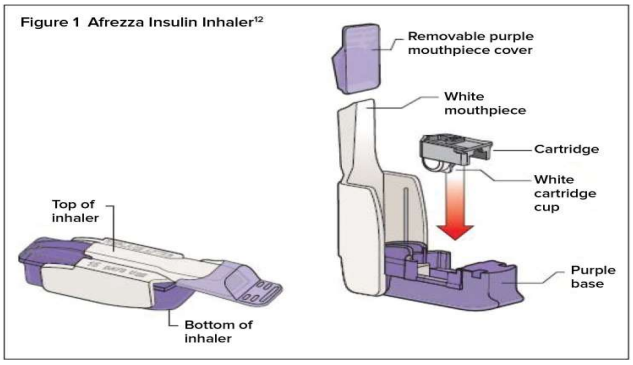
It contains recombinant human insulin dissolved with powder (fumaryl diketopiperazine). Once inhaled, technosphere insulin is rapidly absorbed upon contact with lung surface. Inhalable insulin is delivered with a thumb size inhaler with a rather increased dosing flexibility. Both components, insulin 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.

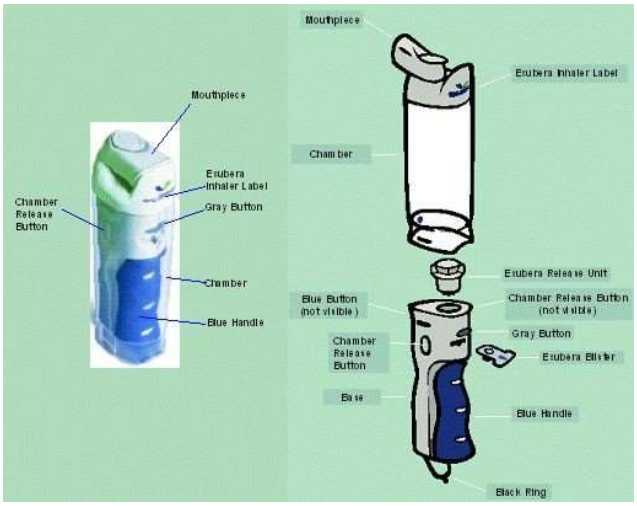
- In one study, Inhaled insulin successfully managed subcutaneous insulin resistance syndrome (rare condition due to rapid degradation of insulin in subcutaneous tissue) [9].
- Literature showed glycemic control as assessed by mean decrease in HbA1c from base line to end point was comparable between 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.

SIDE EFFECT

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.

*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.





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.

Although Exubera was unable to succeed, Afrezza still has a chance to positively affect patient care, but time is of the utmost importance. As new and emerging therapies and medical devices provide easier, safer, and more discreet options for patients, Afrezza will continue to face an uphill battle for success. The experience of the last 80 years in millions of patients has shown that the treatment of diabetes mellitus with subcutaneously administered insulin is relatively safe. However, beside the specific aspects of bioavailability and bio effectivity discussed before, the aspects of tolerability and toxicity must be once more investigated for the inhalant therapy with insulin. In principle, not only insulin, but also absorption enhancers might cause adverse effects in the lung.

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The heading should be treated as a 3rd level heading and should not be assigned a number.

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