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Clinical evaluation of inhaled insulin ☆

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Abstract

Diabetes affects over 18.2 million individuals in the United States alone. Current therapy to treat type 1 diabetes relies on subcutaneous insulin administration either by injection or continuous infusion. In addition, patients with type 2 diabetes who fail lifestyle intervention and oral therapy require subcutaneous insulin. Optimal injection protocols to achieve tight metabolic control often prove burdensome to patients. Thus, development of pulmonary insulin delivery to supplement and/or replace subcutaneous insulin injections may be an effective alternative, allowing patients to achieve intensive diabetes management. This review will discuss the devices in development for the delivery of inhaled insulin. In addition, the efficacy of inhaled insulin in both type 1 and type 2 diabetic populations will be discussed. Finally, the available safety data with respect to the unique pulmonary effects of inhaled insulin will be covered.

Keywords: Type 1 diabetes; Type 2 diabetes; Insulin; Inhalation; Hemoglobin A1c; Lung; Glycemic control; Diabetes; Insulin administration; Drug administration routes

Contents

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1. Introduction

Diabetes is a disease characterized by inadequate insulin supply or ineffective endogenous insulin activity. Insulinopenia, whether actual or relative, leads to hyperglycemia and micro- and macrovascular complications. Diabetes can be broadly divided into two categories — type 1 (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is characterized by severe insulin deficiency as a result of autoimmune pancreatic islet β-cell failure. T1DM classically presents in childhood or adolescence (thus, the prior eponym Juvenile Diabetes), and is characterized by hyperglycemia with susceptibility to ketosis. T2DM is characterized by peripheral tissue resistance to insulin and inadequate insulin secretion. Insulin resistance leads to increased insulin secretion; however, the β-cells fail to maintain this hypersecretory state, and hyperglycemia results. Patients with T2DM usually do not develop ketosis. T2DM typically presents in overweight/obese individuals older than 40 years of age. However, there is a recent trend towards earlier development of T2DM in younger age groups, particularly children [1].

Prior to the discovery of insulin in the early 1920's by Banting and Best [2], diabetes was associated with significant mortality. Currently, the primary mechanism for maintaining adequate blood sugar control in T1DM is through subcutaneous administration of insulin either via syringe or continuous subcutaneous insulin infusion (CSII) via insulin pump. For patients with T2DM whose diabetes cannot be adequately controlled with lifestyle intervention (weight loss and diet) or with oral agents that augment β-cell insulin secretion (secretagogues) or improve peripheral insulin sensitivity (biguanides and thiozolidinediones), insulin therapy must be added. Large scale trials such as the Diabetes Control and Complications Trial (DCCT, T1DM; [3]), and United Kingdom Prospective Diabetes Study (UKPDS, T2DM; [4,5]) have demonstrated that improved metabolic control through intensive management of blood sugars decreases the risk of macro- and microvascular complications of diabetes. Intensive therapy in T1DM involves multiple daily injections (3–6 injections per day) or CSII along with frequent blood sugar monitoring and attention to diet. In the DCCT, the intensive therapy group achieved statistically significant decreases in median glycosylated hemoglobin (HbA1c) compared to patients receiving conventional therapy with twice daily insulin injections [3]. The improved metabolic control translated into reductions in both the development and progression of diabetic retinopathy, nephropathy, and neuropathy — all markers of diabetic microvasular complications. In UKPDS, each 1% reduction in HbA1c with intensive therapy led to significant reductions in risk for any diabetes-related end-point including death, myocardial infarction, and microvascular complications [6]. In