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Pulmonary Insulin Delivery: Challenges and Current Status

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Abstract:
Insulin is usually administered to diabetic patients through subcutaneous injection. However, the various problems are encountered with subcutaneous insulin injection. Insulin cannot be administered via the oral route due to rapid enzymatic degradation in the stomach, inactivation and digestion by proteolytic enzymes, and poor permeability across intestinal epithelium .Hence various alternative routes for insulin delivery have been investigated. The most promising alternative route of insulin administration seems to be pulmonary delivery by inhalation. However, the issue of short duration of action of drugs delivered through this route has continued to challenge drug formulators and various strategies have been developed. This review gives a detailed, overview of the available literature on the safety and efficacy of inhaled insulin in pre-clinical and clinical trials. Additionally, the potential risks of inhaled insulin, in particular concerning insulin antibodies and lung function parameters will be discussed.

INTRODUCTION:

Diabetes is a chronic progressive disease, which can lead to complications such as kidney failure blindness and foot amputation, and it is also a major risk factor for coronary heart disease and stroke. There are two main types of diabetes, type 1 and type 2. Type 1 accounts for 15% of people with diabetes in England and develops most frequently in children, young people and young adults. Type 2 accounts for the rest and is most commonly diagnosed in adults over the age of 40, although it is increasingly being diagnosed in younger people. On average, life expectancy is reduced by more than 20 years in people with type 1 diabetes and by up to 10 years in people with type 2 diabetes [1]. Insulin is usually administered to diabetic patients through subcutaneous injection. However, the problems encountered with subcutaneous insulin injections are pain, allergic reactions, hyperinsulinemia, and insulin lipodystrophy around the injection site .[2] Oral delivery of Insulin as a non-invasive therapy for Diabetes Mellitus is still a challenge to the drug delivery technology, since it is degraded due to the presence of enzymes in the acidic environment of stomach and also its absorption through the gastrointestinal mucosa is questionable.[3] Generally, peptides and proteins such as insulin cannot be administered via the oral route due to rapid enzymatic degradation in the stomach, inactivation and digestion by proteolytic enzymes in the intestinal lumen, and poor permeability across intestinal epithelium because of its high molecular weight and lack of lipophilicity [4-6] Alternative routes for insulin delivery that have been investigated include intrapulmonary[7] intrauterine[8]ocular, nasal,[9] buccal,[10]and transdermal[11] systems. However, results to date indicate problems related to poor absorption, high proteolytic degradation, and/or variable delivery times. Consequently, bioavailability is low, and response times are difficult to predict accurately.

Since the discovery of insulin over 80 years ago, investigators have sought to develop a pulmonary route of insulin delivery. Major absorption of drugs intended for systemic action after pulmonary delivery occurs from the deep alveolar region. The respiratory tract can be categorized into two major regions: the upper respiratory region called the conducting zone and the lower respiratory region termed the respiratory zone. Nasal cavity, sinuses, nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles comprise the conducting zone while the respiratory bronchioles, alveolar ducts and alveolar sacs comprise the respiratory zone. [5]

The pulmonary route of administration offers several advantages. The lung offers nearly ideal conditions for the absorption of peptides including a vast (in humans 50 - 140 m^2, ~500 millions of alveoli) and well-perfuse

absorptive surface area (~5 l blood/min, pulmonary capillary blood volume ranging from 100 to 140 m^2 [12, 13], a thin alveolar-capillary barrier, and the absence of both degrading peptidases (in contrast to e.g. the gastrointestinal tract) and a "first pass metabolism". In addition, the alveolar epithelium has permeability that allows for rapid absorption of solutes. Because the mucociliary clearance of the alveolar lung tissue is slower than that of the bronchiolar tissues, the alveoli provide a greater opportunity for the absorption of larger molecules (eg, insulin) and hence there is renewed interest in administrating insulin by the intrapulmonary route. **[14]** Studies have shown that particle size should be between 1 and 3 micrometers in diameter for optimal deposition in the lung, and that dry powder formulations can deliver more active drug in a single inhalation than liquid aerosol formulations patient-controlled variables (eg, inhalation flow rate, inhaled volume, and duration of inhalation) also need to be controlled for optimal deep-lung insulin delivery.[12,13,15] Growing attentions have been paid to the pulmonary route for systemic delivery of peptide and protein drugs, such as insulin. Advantages of this non-injective route include rapid drug deposition in the target organ, fewer systemic side effects and avoiding first pass metabolism. However, sustained release formulations for pulmonary delivery have not been fully exploited till now. Recently a novel dry powder inhalation (DPI) system of insulin loaded solid lipid nanoparticles (Ins-SLNs) was investigated for prolonged drug release, improved stability and effective inhalation. [16]

BIOAVAILABILITY AND BIOEQUIVALENCE:

Insulin in a given aerosol (independent from powder or liquid) is unevenly distributed among particles with various sizes and deposition properties. As larger amounts of insulin can only be absorbed in the alveoli, insulin particles must be within a narrow range to reach the deep lung with the optimal particle size being in the range of 1-5 µm.[17, 18] The bioavailability values for inhaled insulin relative to subcutaneously administered insulin have mainly been in the 8-15% range.[19,20,21] The reasons for the loss of approximately 85-90% of insulin during inhalation are not fully understood, but it seems to be due to a combination of several reasons. [22,23]

- Part of the insulin remains in the (drug) container after inhalation.
- Another part adheres to the inner surfaces of the inhaler.
- Larger particles are deposited in mouth and throat, and in the bronchial tree.
- Smaller particles are exhaled without being deposited.
- Insulin deposited in the alveoli is degraded by macrophages and peptidases

Pre-clinical studies:

Animal studies have been conducted to characterize the pharmacology and disposition of insulin given by inhalation. A majority of the published research on lung absorption of insulin resulted from experiments using rabbits. In 1971, Wigley, et al. [23] exposed rabbits by head-only inhalation to aerosols of solutions of regular insulin (80 U/mL) in a closed system which contained ~ 400 U of insulin aerosol. Over the course of two hours after inhalation of the insulin aerosols, blood glucose levels dropped from ~ 150 to ~ 90 mg/dl. Colthorpe et al. [24] Pillai, et al[25], repeatedly treated rhesus monkeys with insulin aerosols and measured pharmacokinetic, pharmacodynamic, and pulmonary physiologic responses. All animals tolerated repeated treatment with insulin aerosols well, and pulmonary function tests were all within the range of normal values.

In summary, inhaled insulin has been demonstrated to be safe and efficacious in animal trials.

Efficacy of inhaled insulin in later phase clinical studies

Recently, several studies with multiple dose applications have been completed that

describe the inhalation of insulin using modern inhalers which create small particle sizes suited for deep lung delivery[26-36]. The viability of longer-term dosing regimens has been reported after recent phase II studies of a dry-powder formulation. Skyler, et al.[45] and Cefalu, et al.[29] showed that in diabetic patients (type 1 and type 2, respectively) inhaled insulin regimens, in combination with a single subcutaneous daily dose of Ultralente insulin, resulted in the same degree of diabetes control as standard subcutaneous insulin regimens. The majority of patients in these studies elected to continue their inhaled insulin. Using the same device and formulation, Weiss et al.[41] showed that the addition of pre-meal insulin improves the glycemic control of type 2 diabetic patients who are failing oral agents. Cefalu, et al. reported stable glycemic control spanning 2 years of inhalation therapy in 83 patients [32]. With the same device, it was demonstrated that both type 1 and type 2 diabetic patients preferred inhaled over s.c. insulin. [31, 42] It has even been shown that the availability of inhaled insulin promotes greater acceptance of insulin therapy in patients with type 2 diabetes –a finding, however, which needs confirmation in a real treatment trial.

Recently published results of long-term (i.e., six months) studies with inhaled insulin in several hundreds of patients showed improved blood glucose control in patients with type 1 diabetes treated with preprandial administrations of inhaled insulin compared with patients on two to three injections of regular and NPH insulin [33]

The AERx® system is a technology platform that, using portable hand held devices, converts aqueous solutions of drugs or biologics into fine respirable aerosols in 1–2 seconds in a highly efficient and reproduciblemanner.[34] Aradigm has demonstrated through laboratory research and more than 50 human clinical trials that their hand-held AERx® pulmonarydrug delivery system is particularly well suited for drugs where highlyefficient and precise delivery to the respiratory tract is advantageous oressential. Our partner, Novo Nordisk, is currently in phase III developmentof AERx® Insulin Diabetes Management System® (AERx®) which delivers insulin to the systemic circulation via the lung.

***Clinical trials*:**

The published data about the results of the phase III trials with Exubera® indicate that the metabolic control achieved is superior compared to oral agents and comparable to sc insulin. This inhaled insulin controls fasting blood glucose more effectively than oral agents or sc insulin. In these trials Exubera® was well tolerated during long-term use, with no increased risk of hypoglycaemia and was preferred by the patients over sc insulin and oral agents. The phase III results confirms the results of the phase II trials.[35-38] Like in the phase II trials, patient's satisfaction was enhanced with inhaled insulin treatment compared with s.c. insulin injections.[39]

SAFETY OF INHALED INSULIN :

Both porcine [29-31] and human insulin [43. 44] have been used in inhalation trials. In general, insulin administration via inhalation has been well-tolerated. In many studies, no adverse events occurred that were attributed to the inhalation. Even in the six months trials the incidence of adverse events was comparable between inhaled and sc insulin treatment [33, 40]. Nevertheless, certain adverse events were attributed to the inhalation of insulin including effects on pulmonary function parameters or coughing, episodes of hypoglycemia, and a rise in insulin antibodies. It has been found that, compared to those taking insulin injections; there is an increase in insulin antibodies in people with type 1 diabetes who take inhaled insulin. A smaller rise in insulin antibodies occurred in people with type 2 diabetes who were treated with inhaled insulin, although this change was not seen in people with type 2 diabetes who had not started any form of insulin therapy. [45]

Clinical studies with inhaled insulin suggest that pulmonary delivery is well tolerated, with a level of safety comparable to that of

subcutaneous insulin. [9] The only significant clinical adverse effect is cough. This cough is generally characterized as mild to moderate in severity, decreases over time and is not associated with a decline in pulmonary function. The two main safety concerns with inhaled insulin are its effects on the lungs and the potential formation of antibodies that might interfere with the action of insulin and/or result in other adverse effects. [46]
As with sc insulin, treatment with inhaled insulin obviously causes hypoglycemia. However, the available long term data on inhaled insulin either shows no difference in the frequency and severity of hypoglycemia between inhaled and sc insulin [47] or a significant reduction in hypoglycemia with inhaled insulin in comparison to sc regular insulin.[49, 50]

LIMITATIONS OF INHALED INSULIN

1. Very little data is available on the long-term safety of inhaled insulin, and particularly its effects on antibody formation and lung function, although more studies are underway. The longest trials so far have been two years.
2. Inhaled insulin will not eliminate injections. People with type 1 diabetes will still need to test their blood glucose regularly and may still need to inject different forms of insulin.
3. Inhaled insulin may not be suitable for people with lung problems.
4. Inhaled insulin will probably be more expensive than subcutaneous insulin.
5. Alterations in lung function were observed in some studies. For example a significant decrease in the carbon monoxide diffusion capacity (DLCO [ml/min/mmHg], changes from baseline) relative to sc insulin was reported in phase III trials with the Exubera inhaler after six months of therapy in patients with type 1 and in type 2 diabetes as noted below [48]

	Inhaled Insulin	***sc Insulin***	***95% confidence Intervals***
Type 1	-0.75	0.229	-1.49;-0.15
Type 1	-1.688	-0.389	-2.03;-0.58
Type 2	-1.046	-0.385	-1.57;-0.04

In phase II and III studies with Exubera® insulin antibody formation was evaluated. Patients with either type 1 or type 2 diabetes experienced a rise in insulin antibody levels rapidly after switching to inhaled insulin. After six months of therapy the percentage of insulin antibody levels (median values; two different studies with type 1 patients) were [51]

	Inhaled insulin	***sc insulin***
Type 1	28	4
Type 1	29	3
Type	2 5.0	1.5

In the patients who stayed on sc insulin administration, no change in insulin antibody levels was observed. The increase was higher in patients with type 1 than with type 2 diabetes.

CURRENT STATUS OF THE DEVELOPMENT OF INHALED INSULIN [54]

The pharmacodynamic effects of insulin formulations administered via the lung are comparable to, or are even faster than, those of subcutaneously injected regular insulin or rapid-acting insulin analogues. The relative biopotency of inhaled insulin is approximately 10%, i.e., the dose of inhaled insulin must be 10 times higher than the dose applied subcutaneously in order to induce a comparable metabolic effect. Clinical trials indicate that metabolic control with this pain free route of insulin administration is at least comparable to that of subcutaneous (sc) insulin therapy. Several inhaled insulin systems are currently in advanced phases of clinical development. These include the following:

The time-action profiles obtained in healthy subjects with inhalation of 6 mg insulin via the dry powder inhaler system Exubera® (being developed by Pfizer Inc. and Aventis Pharma in conjunction with Nektar Therapeutics), were compared with those of sc injection of the rapid-acting insulin analogue insulin lispro and of regular insulin (both 18 U). The comparison showed that the onset of action with the inhaled insulin powder was even more rapid than that of the rapid-acting insulin analogue [55]

Mann Kind is starting phase 3 clinical trials on its Technosphere system, which uses a dry powder form of insulin with a proprietary inhaler systems that use a liquid formulation (Novo Nordisk and Aradigm; Kos Pharmaceuticals) a novel dry powder preparation, formulated as 'techno-spheres', in which insulin is mixed with a small organic molecule, which are transformed into microspheres with a diameter of about 2 mm – facilitates very rapid insulin absorption from the lung (MannKind Biopharmaceuticals) other systems that use a dry powder insulin formulation (Eli Lilly and Alkermes). [54]

It was the invention of modern handheld inhalers, allowing the generation of an aerosol with an adequate particle size distribution, some 15 years ago, which started the rapid development of pulmonary insulin administration. A considerable number of inhalers differing in construction, size, weight, handling, etc. are currently in the clinical phase of development. In the first study investigating the time-action profile of a pure dry powder insulin preparation (99 IU), inhaled with a small inhaler was employed in a glucose-clamp study in healthy male volunteers. It showed that the onset of action was more rapid than that of sc regular insulin and the duration of action comparable. [56] The addition of an absorption enhancer (a bile salt) led to considerable changes in the time-action profile of the inhaled insulin powder aerosol, i.e., the onset of action was substantially more rapid than with the previous formulation without enhancer, and the metabolic effect in the first two hours after inhalation was significantly greater. [57]

The pharmacodynamic properties of Technospheres/Insulin (MannKind [former PDC; Valencia, CA, USA]) showed a much more rapid onset of action than after sc administration of regular insulin.[6] Moreover, the relative biopotency over six hours of the inhaled insulin was nearly twice as high as the biopotency observed with other insulin formulations.[58]

Use of large porous particles loaded with insulin, which are stable at room temperature, allows Alkermes (Cambridge, MA, USA) in cooperation with Eli Lilly (Indianapolis, IN, USA) to construct small, elegant inhalers. Clinical-experimental studies performed with this approach showed that inhalation of 84, 168 and 294 IU by means of this powder-based system induced a fast onset of action in comparison to sc regular insulin and a linear dose-response, with a biopotency of 18%.[59]This system is currently in phase II trials. The company KOS (Miami Lakes, FL, USA) has developed a novel regular insulin preparation which is applied to the lungs with a simple, inexpensive, and strictly mechanically working metered-dose inhaler (MDI). induced a rapid onset of action in comparison to sc injection or 10 IU regular insulin and a linear dose-response relationship [60] Bio potency ranges between 10 and 15% compared to sc regular insulin. Currently the first small phase II studies with this inhaler have been started.

As advances in technology emerge, more opportunities arise to assist health care professionals with more productive ways of providing better care to patients by exploring other options for drug delivery. The formulation of various innovative drug delivery systems is a prospering industry in the United States. Furthermore, through these new developments, the pulmonary route of drug delivery may indeed be beneficial to a host of patients afflicted with many other systemic diseases

Encapsulation or entrapment of proteins in biocompatible polymeric devices represents

the most widely reported systems for the controlled release of peptides and proteins. Polymers such as PLGA, PLA, PEG and chitosan have been applied as delivery vehicles in pulmonary delivery of proteins, producing sustained systemic therapeutic activities. Proteins such as Insulin and deslorelin have either been conjugated to PEG or encapsulated in PLGA, PLA or chitosan for controlled release activity via the pulmonary route. Insulin has been encapsulated in PLGA by emulsion solvent evaporation forming particles of mean diameter of 400nm .Following the administration of these nanospheres into the trachea of a fasted guinea pig, the blood glucose level was reduced significantly and the hypoglycaemia was prolonged for 48 hrs compared to the nebulized aqueous solution of insulin .The use of protein microcrystal has been discussed as a potential means for controlled release delivery of therapeutic proteins. In their recent research demonstrated successful and sustained reduction of blood glucose level following the administration of nebulised liposome encapsulated insulin to diabetic mice. Reduced blood glucose levels were observed to be significantly lower when comparing liposome encapsulated insulin to insulin and liposome administered separately .[61]

BENEFITS OF PULMONARY DRUG DELIVERY:

1. May increase patient acceptance and compliance due to a non invasive route of administration as an alternative to injections.
2. Rapid onset of action without first pass metabolism, as in the utilization of oral or subcutaneous drug delivery system.
3. Providing greater dosing capacity.
4. More efficient drug delivery using less amount of drug.
5. Decrease the incident of systemic side effect for local lung infection.
6. Inhaled insulin provides a prandial metabolic control comparable to sc regular insulin

CONCLUSION:

Pulmonary insulin as a non-injective route include rapid drug deposition in the target organ, fewer systemic side effects and avoiding first pass metabolism. Clinical-experimental studies show that the time-action profile of inhaled insulin offers some advantages over that of sc regular insulin by showing a more rapid onset of action. The duration of action of inhaled insulin is in-between that of sc regular insulin and insulin analogues. Therefore, inhaled insulin seems to be an attractive alternative to sc insulin preparations for prandial insulin substitution, in particular for patients with type 2 diabetes mellitus who are often reluctant to take sc injections. Advantages have been demonstrated for inhaled insulin with regard to treatment satisfaction in numerous studies, more efficient drug delivery using less amount of drug and decrease the incident of systemic side effect for local lung infection. Potential risks of inhaled insulin involve the induction of insulin antibodies and subtle deteriorations in lung function. Clinical studies with inhaled insulin suggest that pulmonary delivery is well tolerated, with a level of safety comparable to that of subcutaneous insulin.

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