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Family Physician Corner

Inhaled Insulin: A Truth or a Fallacy?

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Injectable Insulin therapy has revolutionized the management and life prospective for diabetics since its discovery in 1922 by Banting and Best[1].

Since then, many forms of insulins have been introduced to the market giving more options for the practicing physician and the chronic patient.

In their ever search for more convenience to the patient and more practicality to the physician, researchers were able to extract and synthesize purer forms of injectable insulin[2]. This, in turn, led to less desirable side effects and more convenient form of delivery. DNA Technology has provided us with the purist form of insulin and hence smaller size needles were used[2].

Nevertheless, the idea of other modes of insulin delivery was very attractive dating back to 1935, when inhaled insulin was first introduced[3]. The brilliant idea was aborted by the unpredictability of inhaled insulin absorption, the individual variability of absorption and its decreased bioavailability[3].

It's not until recently when major studies like DCTT and UKPDS have recommended that tight control through multiple insulin injections is necessary to prevent morbidities and improve mortalities among diabetics[4]. The idea of alternative mode of insulin delivery was revived.

In 1981, Wigley et al showed that delivering pork-beef insulin using a nebulizer produced a prompt increase in plasma insulin and hypoglycemia[3].

The highly vascular alveolar bed measuring about 140m.sup[2] is a very appealing alternative to the skin as a mode of insulin delivery[5]. The lungs are superior over the gastrointestinal tract as a mode of insulin delivery because they lack the digestive enzymes and drugs don't pass through the liver and get exposed to first pass metabolism[6].

The exact mechanism of insulin absorption in the lungs is to be discovered. Nevertheless, it's proposed that alveolar absorption of insulin involves transcytotic and paracellular mechanisms[3].

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Inhaled insulins were first administered using traditional asthma drug delivery devices. These include nebulizers, metered-dose inhalers and dry-powder inhalers. Being efficient in the treatment of asthma, these conventional devices failed to deliver insulin to the more deep and remote alveoli, the earliest obstacle to inhaled insulin therapy; therefore, develop a device capable of delivering insulin to the deep lung is needed[5].

Problems concerning inhaled insulin delivery include type of propellants used, air flow speed, intra and extra alveolar drug loss, particle size, drug clearance, drug deposition, drug absorption and the potential effect of concomitant respiratory disease[6].

For optimal alveolar delivery and deposition, particle size should be between 1-3μm. If smaller sized particles are used it will be lost before it reaches the alveoli and if bigger it will condensate around the device[7].

The bioavailability of insulin was enhanced by using the powdered form rather than the liquidized form[6].

Types of inhaled insulin devices

Exubera

This system developed by nektar is supposed to deliver regular insulin in a dry-powdered form (less than 5 μm in diameter) to the alveoli[3]. The insulin dry powder is packaged into a single-dose blister containing 1 or 3 mg. The 1 mg blister delivers 3 units of regular insulin[6]. Reproducible and consistent delivery of the insulin is insured by a pneumatic mechanism where the insulin powder is discretely dispersed in air chamber[6].

Like the asthma device, the insulin is inhaled slowly at the beginning of deep inspiration[7].

Table 1. **Comparison between the two most studied insulin inhaler devices***

	Exubera	*AER$_x$*
ManfacturingCompany	Nektar, Aventis and Pfizer	Aradigm and Novo Nordisk
Stage of device development	Late phase III	Early phase III
Type of Inhaled Insulin	Dry powder insulin packaged in individual blisters of 1-3mg	Liquid insulin packaged in individual strips dosed in single units
Minimum dose	3units (1mg)	Not yet established
Mechanism of action	Purely mechanical trigger	Uses microprocessors to

	activated; no battery or chip. Used in mouth like an asthma inhaler.	produce the correct rate and depth of breathing ensuring consistent delivery regardless of breathing capacity.
Comparison to subcutaneous regular Insulin	Faster absorption and onset of action Comparable pharmacodynamic and glycaemic control in both type 1 and 2 D.M	Faster absorption and onset of action. Comparable pharmacodynamic and glycaemic control in type 1.
Patient Satisfaction	Improved	Improved
Size of device	6 inches tall in closed position(size of mechanical flash light)	7 by 4 by 1.5 inches
Pure insulin concentration per particle	95%	1-2%
Size of insulin particle	< 5 μm	2-3μm

** Adopted from refernce 6 with modification.*

AERx

This device developed by Aradigm uses liquidized form of insulin in 1-3μm in diameter particles. The correct, consistent and reproducible dose is insured by microprocessors[8]. This delivers insulin to alveoli regardless of patient's breathing cycle and abilities.

Recently, another inhaler system was introduced. This system is called the technosphere[3]. It's in phase 1 trial but it's promising since it employs a system of ordered lattice array of technosphere dry powder particles and recombinant human insulin [6].

Evidence-Based Trials

In phase II Clinical Trials, three studies worth mentioning (Table 2)[9]. The first one compared regular inhaled insulin versus long acting injectable subcutaneous insulin in type II Diabetes Mellitus. A reduction of 0.7% in HbA1c in both groups was noted at the end of the 3 months period.

Table 2. **Summarizes some trials to verify the effectivness of inhaled insulin used***

D.M type	**Number of patients**	**Duration of the study**	**Change in HbA_{lc}**
Type II	51	3 months	0.7% decrease in both inhaled and subcutaneous

			insulin groups.
Type II	298	6 months	Both subcutaneous and inhaled insulin were comparable
TypeI	73	3 months	Subcutaneous insulin led to 0.8% decrease in HbA1c. Inhaled insulin led to 0.64% decrease in HbA1c.
Type II	62	3 months	Oral agents led to 0.13% decrease in HbA1c. Oral agents and inhaled insulin led to 2.28% decrease in HbA1c.

** Adopted from refernce 6.*

In the second study, type II patients treated with oral hypoglycaemic agents were randomized to either receive their preexisting treatment or the oral agents plus inhaled insulin[10]. At the end of 3 months period, the first group experienced 0.13% decrease in HbA1c while the group on oral agents plus inhaled insulin experienced 2.28% reduction.

The third study was on type I diabetics in which one group received inhaled insulin plus long acting subcutaneous insulin and the second group received their pre study regimen[11]. No statistically significant difference was noted in HbA1c at the end of the three months period.

The adverse events of inhaled insulin are very much comparable to those of subcutaneous insulin. The only exception is cough which wanes away after continuous use[2].

The level of anti insulin antibodies seems to rise after inhaled insulin use. No studies have yet compared the rise in insulin antibodies in inhaled insulin-using patients to the rise in antibodies in subcutaneous insulin-using patients[6].

Some studies have reported decrease in pulmonary function tests after inhaled insulin usage[2]. Inhaled insulin dosage should be adjusted for smokers as smoking was reported to greatly enhance insulin absorption[2].

Patient satisfaction and morals are greatly enhanced with inhaled insulin treatment compared with injectable insulin[12].

In conclusion, it is not premature to say that we have enough evidence that inhaled insulin usage is a dream came true rather than a fallacy. The advantages of its use far outweigh the rarely documented side effects and precautions. Patient demand an alternative mode of insulin administrations and this has made it mandatory to adopt these new modalities.

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