A hand is visible in the bottom left corner, holding a thin green stem with a small, white, fluffy seed head (dandelion) at the top. The background is a light, warm-toned gradient.

Unknown Health Risks *of Inhaled Insulin*

By T.R. Shantha, MD, PhD, FACA

Fear of needles and the inconvenience of administering insulin injections have created a burgeoning demand for alternative methods of treating diabetes. An apparent breakthrough arrived with the development of an insulin preparation that required no needles, but instead could simply be inhaled.

While the FDA has deemed this novel insulin preparation safe and effective, many questions regarding its long-term health effects remain unresolved. Here, we discuss the use, safety, and potential risks of insulin inhalation preparations. > > >

INSULIN AND THE ETIOLOGY OF DIABETES

Insulin is a hormone that is essential for human life. It works by interacting with the insulin receptors on cell membranes to facilitate the entry of glucose and other nutrients into cells for energy production. Insulin thus facilitates various cellular metabolic functions and promotes cell division, while removing excess sugar from the blood.

Type 1 diabetes is characterized by a lack of insulin in the blood due to lack of its production in the pancreas (specifically, in the islets of Langerhans). In type 2 diabetes, the pancreas does produce insulin, but the body's cells are resistant to insulin's action—it is as if the doors that allow glucose to move from the blood into the cells are shut. The result is high levels of unused insulin and glucose in the blood—the hallmarks of early-stage type 2 diabetes. In the later stages of type 2 diabetes,

the pancreas fails to secrete enough insulin, and the patient becomes reliant on either drugs that artificially stimulate pancreatic insulin secretion, or on exogenously administered insulin.

Presently, type 1 diabetes is treated with daily insulin injections, whereas type 2 diabetes is treated with oral anti-diabetic pills, either alone or in combination with insulin shots. Other safe modalities to curtail, control, and cure diabetes are under intense research. The most recent innovation in diabetes management is the introduction of insulin for inhalation, rather than for injection.

DEVELOPMENT OF INHALED INSULIN TO TREAT DIABETES

Based on today's epidemic of diabetes, there is a large and growing demand for insulin drugs. However, the pain, inconvenience, and disruption of lifestyle associ-

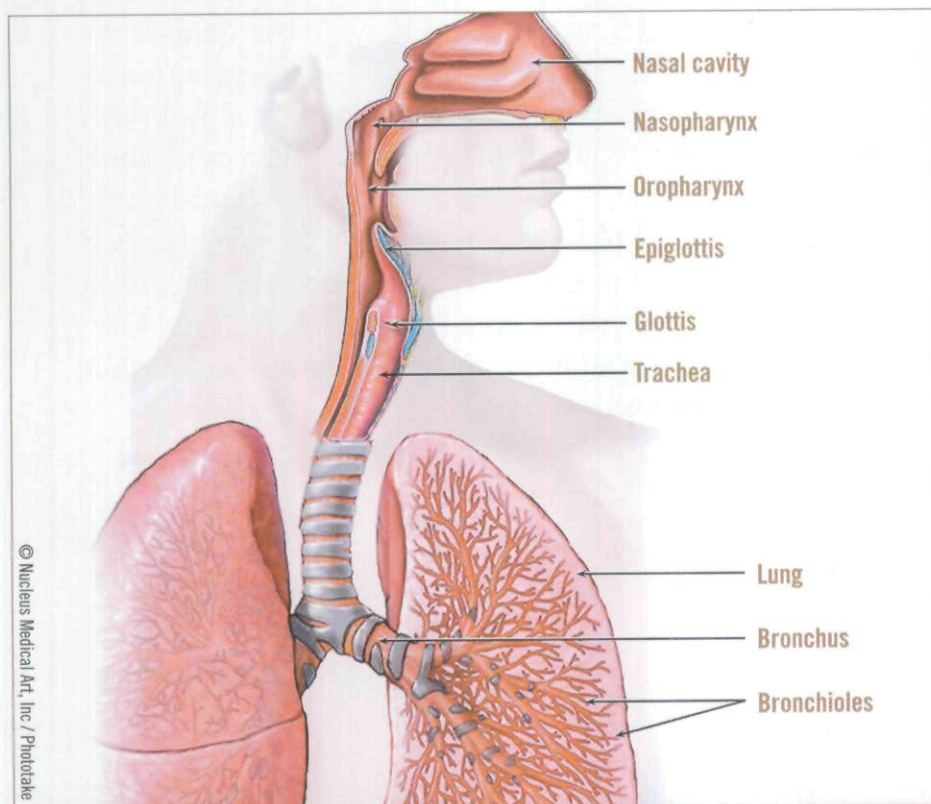
ated with multiple daily insulin injections leads many patients to abandon their doctor-recommended treatment plans. As a result, many patients fail to achieve effective management of their condition. To eliminate pain and improve patient compliance—and thus treatment outcomes—increasing research has focused on alternatives to subcutaneous (SC) insulin injections. Some of the areas of investigation include: aerosolized insulin for inhalation, oral insulin, insulin-producing stem cell implantation, and insulin delivery pumps.

The first inhalation insulin has now been approved for use in US and Europe, and numerous similar products are on the horizon. This novel device delivers a powdered form of insulin to the alveoli of the lungs, where, since the lung is a large microvascular organ, insulin is absorbed into the bloodstream.¹

DISTRIBUTION OF INHALED INSULIN, INSULIN RECEPTORS, AND CANCER

The inhaled form of insulin is effective only when the administered dose is three to ten times the amount given by subcutaneous injection, because little more than 10% of the inhaled insulin reaches the alveoli.^{2,3} The interval between the administration of insulin and the onset of glucose-lowering activity is about 10 to 20 minutes. Given its rapid onset of activity, inhaled insulin is suitable for preprandial (before meal) but not for long-term basal (baseline) use.

Tight glucose control, however, may come at a price. One area of potential concern regarding inhaled insulin is the possible effects on the tissues that it comes in contact with on its way to the alveoli, such as the linings of the mouth, throat, tongue, cheeks, gums, tonsils, trachea, bronchial tree, vocal cords, larynx, nose and nasal air sinuses, and olfactory mucosa (which has a direct connection to the brain). Furthermore, since insulin is a weak growth factor, there is also the potential concern that inhaled insulin could support

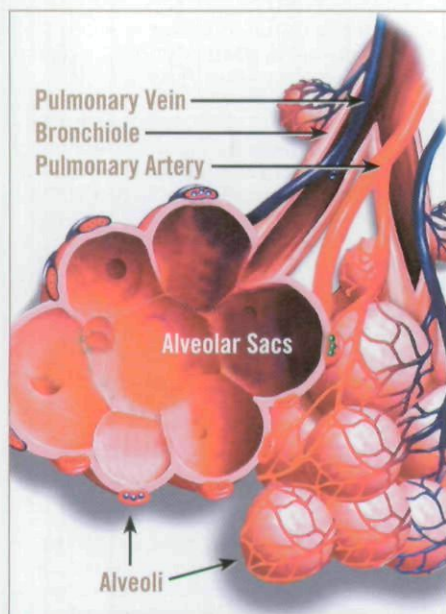


The Respiratory System.

Diagram of the nasal, pharyngeal, oral, and respiratory passages.

Inhaled insulin is diffused via the alveoli into the bloodstream.

Many tissues are exposed to inhaled insulin before it reaches the alveoli in the lungs.



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POTENTIAL HEALTH RISKS OF INHALED INSULIN THERAPY

Other questions still remain unresolved about the potential health risks of inhaled insulin. Among the documented and possible health risks of insulin inhalation therapy are:

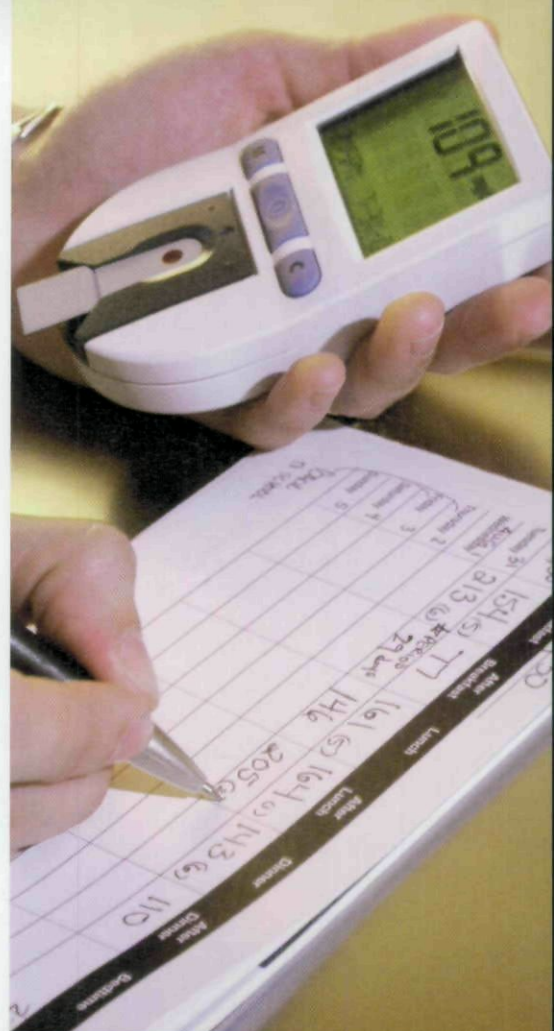
1. Increased risk of respiratory tract irritation, causing cough, shortness of breath, sore throat, and dry mouth.¹²
2. Development of hypoglycemia, with adverse outcomes in those who exercise immediately after inhalation and those who smoke. These effects may occur due to the rapid absorption of inhaled insulin from the alveoli.¹³⁻¹⁵
3. Exacerbation of existing conditions in asthmatics who require more inhaled insulin to control their blood sugar.¹⁶ Furthermore, inhaled insulin could lead to airway smooth muscle contraction, which could precipitate or exacerbate chronic obstructive pulmonary disease or episodes of asthma.¹⁷
4. Alveolar thickening, poor gas exchange, pulmonary hypertension, or pulmonary fibrosis. Additionally, inhaled insulin could cause adverse effects in people with pre-existing respiratory diseases such as chronic bronchitis, tuberculosis, tumors, and other chronic lung afflictions.¹⁸
5. Increase in insulin antibodies. In one study, inhaled insulin increased the level of insulin antibodies in the body from baseline levels of 6% to 35%.¹⁹ This could have the adverse effect of retarding the action of soluble insulin in the blood, since the removal of an insulin immune complex could make less insulin available to lower blood sugar.

aberrant cell growth, and potentially even trigger or support cancer.

Scientists have noted that those with elevated blood sugar due to type 2 diabetes and other conditions are more prone to develop certain types of cancers than the healthy population.⁴ Numerous cancers, and even non-cancerous fibrous tumors, have more than the normal amount of insulin receptors to facilitate the entry of large amounts of glucose into the tumor cells, thus promoting their growth, multiplication, and spread.⁵⁻¹⁰

Another important uncertainty about treatment with inhaled insulin is therefore the potentially increased risk of lung cancer. Studies of human bronchial epithelial cells suggest that insulin-receptor activation is in itself insufficient for malignant transformation. However, once malignant transformation has been induced by other agents, the insulin receptor pathway is thought to promote malignant progression of these cells.¹¹

Since inhaled insulin comes in contact with so many tissues, it is crucial that future research examines its impact on normal, pre-cancerous, and cancerous cells of the upper respiratory and digestive systems.



Inhaled Insulin: What You Need to Know

- Insulin allows glucose to enter cells, and is thus essential for cell growth and energy production. Since people with diabetes either do not produce enough insulin, or their cells are not sensitive to its effects, insulin is an essential cornerstone of diabetes treatment.
- Until recently, the only way to administer insulin was via injection. A recent breakthrough came with the introduction of an insulin preparation that can be inhaled.
- While many people are embracing this new form of FDA-approved insulin, its long-term safety has not yet been established. Since insulin acts like a mild growth factor, it is possible that inhaled insulin could stimulate unwanted tissue growth in the respiratory tract.
- Inhaled insulin is not approved for use in pregnant women, children, or adolescents. Smokers and patients with underlying lung diseases should avoid using inhaled insulin.

6. Unknown long-term effects of supraphysiologic doses of insulin in the human lung or on neoplastic lung tissue. It is possible that insulin could stimulate unwanted tissue growth in normal and precancerous cells, which could lead to genetic defects and ultimately to cancer.
7. Potentially increased tumor incidence in the tissues of the respiratory tract, although no evidence of this has been presented to date.

The true health risks could take a long time to come to light, as occurred with other drugs such as Vioxx® (an anti-inflammatory) and Avandia® (an oral anti-diabetic drug). In addition to the eye-opening health risks of inhaled insulin, it is more expensive than other insulin preparations.

SHOULD YOU USE INHALED INSULIN?

I recommend that inhaled insulin should not be used in smokers or in patients with underlying lung diseases such as asthma or chronic obstructive pulmonary disease. Until the drug's full health risks are known, I further discourage its use in those with precancerous lesions (such as polyps, dysplasia, or the leukoplakia that can accompany tobacco use). Inhaled insulin is not approved for use in pregnant women, children, or adolescents. I hope that the FDA and drug companies involved in licensing and developing an inhaled method of insulin delivery will fully investigate these health risks and concerns on a post-approval surveillance basis. The future of insulin delivery with the fewest side effects may come from development of slow-release injectable insulin lasting days to weeks with a single shot, or from implantation of insulin-producing stem cells. ■

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