INHALED INSULIN IN PRIMARY CARE

By

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Inhaled Insulin in Primary Care

Abstract

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According to the American Association of Clinical Endocrinologists, well over half of the population with diabetes receives inadequate care. Research indicates that providers as well as patients are reluctant to begin subcutaneous insulin therapy until absolutely necessary. Human inhaled insulin powder has been shown to be safe and efficacious when used as pre-prandial therapy in patients with type 1 and type 2 diabetes. HIIP gives nurse practitioners a new option that may improve their patients acceptance of insulin therapy, and improve glycemic control. The purpose of this article is to expand providers' knowledge and comfort with using HIIP as an alternative to injectable insulin.
Inhaled insulin, an innovation with the potential to transform the management of Type 1 and Type 2 diabetes.

Every 21 seconds someone is diagnosed with diabetes\(^1\). Nationally, 67% of people with type 2 diabetes do not have control of their blood sugar, and have hemoglobin A1C (A1C) levels exceeding the American Association of Clinical Endocrinologists (AACE) recommended goal of 6.5% or less.\(^2\) Inadequate management of diabetes places many people at risk for microvascular and macrovascular complications. Because of the pain, inconvenience, and lifestyle disruption associated with insulin injections, many patients with diabetes resist treatment regimens that require multiple daily injections.\(^3\)

Scientific knowledge has advanced to enable the development of inhaled insulin.\(^4\) It is a form of diabetes medication administered via the pulmonary system that studies have shown to be efficacious in the treatment of both type 1 and type 2 diabetes. This article provides an overview of research related to the potential for human inhaled insulin powder (HIIP) to improve glycemic control in patients with diabetes. Nurse practitioners (NPs) can offer HIIP as another choice for effective pharmacological therapy in patients with diabetes.

**History of inhaled insulin**

Approximately 80 years have been devoted to the modification, purification, and production of human inhaled insulin. The concept of inhaled insulin was first investigated in Germany in 1925 where the use of a nebulizer to deliver insulin was initially explored.\(^5\) Insulin is a protein macromolecule with a large particle size that is not easily absorbed into the alveoli of the lung.

Many years of research resulting in failures to achieve euglycemia with intrapulmonary insulin delivery were likely due to underdosage, probably arising from the loss of drug in the
oopharynx or in the delivery device, secondary to large particle size. Since that time, investigators have continued to focus on the development of non-invasive routes to deliver proteins such as insulin. Non-invasive routes include transdermal, oral, intranasal and intrapulmonary. While the nasal cavity is more accessible, it has a decreased surface area for absorption compared to that of the alveolar region of the lung. Intranasal insulin could also be rapidly moved to the back of the nasopharynx by the mucocilliary mechanisms in the nose, and swallowed. Insulin deposited in the lungs has a longer residence time because mucocilliary clearance mechanisms are minimal. Transdermal and oral delivery routes face more challenges due to poor absorption, but continue to be a focus of research. There is currently one FDA approved HIIP that entered the market in late 2006, and at least 6 new pulmonary insulin drugs and delivery systems that are in active development.

Importance of Inhaled Insulin as a Treatment Option

People with type 1 diabetes achieve glycemic control with multiple daily injections of basal, intermediate or long acting insulin, and bolus, short-acting insulin. People with type 2 diabetes who fail to achieve glycemic control with lifestyle changes and diet modification may eventually need insulin. The AACE reports that only 33% of the population with diabetes achieves optimal A1C goals. People with diabetes, not well managed on maximum oral medication, need sufficient education to understand the benefits of subcutaneous (SC) insulin in managing their diabetes. However, insulin injections, the pain associated with them and lifestyle changes that would occur following initiation of insulin treatment may be a deterrent to beginning SC insulin therapy. Research also indicates that providers as well as patients are reluctant to initiate insulin therapy.
HIIP may be a long-awaited alternative to current SC insulin providing a significant advantage in terms of patient acceptance, satisfaction and adherence\textsuperscript{5}. Clinical studies indicate that when people with type 2 diabetes were educated about HIIP as an alternative to SC insulin, a significant number chose HIIP as adjunctive or monotherapy in glycemic control.\textsuperscript{11} Evidence also suggests that there is a greater potential for improved glycemic control with HIIP, therefore minimizing the microvascular and macrovascular complications of diabetes.\textsuperscript{11}

**The Pharmacokinetics and Evidence of Inhaled Insulin Efficacy**

HIIP is delivered to the lungs where it is rapidly absorbed into the blood stream. Compared with SC regular insulin, inhaled insulin is more rapidly absorbed, eliminated, and has a more rapid glucose-lowering effect.\textsuperscript{8}

In its early pharmacokinetic profile, HIIP demonstrated a rapid initial absorption comparable with that of SC lispro (Fig. 1).\textsuperscript{12}

**Figure 1: Pharmacokinetic Profile of Lispro and HIIP**


Available at: [http://care.diabetesjournals.org/cgi/content/full/28/10/2400](http://care.diabetesjournals.org/cgi/content/full/28/10/2400)

One study confirmed that the time to maximal insulin levels averaged 24 minutes with HIIP versus an average of 106 minutes for SC injection of regular insulin. In addition to a faster onset, inhaled insulin has a slightly longer duration of effect compared to that of rapid acting insulin analogues given subcutaneously.

Evidence suggests that inhaled insulin before meals works the same as SC insulin before meals in people with type 1 and type 2 diabetes. A 6 month randomized comparative trial to evaluate the efficacy of HIIP on A1C and post-prandial glucose measurements showed relatively similar A1C control between inhaled insulin and SC lispro insulin (Fig 2). HIIP shows much better control over fasting plasma glucose versus subcutaneous lispro (Fig 2).

Figure 2: Efficacy of HIIP on A1C and Postprandial Blood Sugars

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Analysis and Evaluation of Research for Type 1 and 2 Diabetes

Research on the efficacy of HIIP has been done using basal and fast acting injectable insulin analogues as well as some oral anti-diabetic medications. People with type 1 diabetes have participated in research to determine whether it would be efficacious to substitute HIIP for pre-prandial (before meals), fast acting or regular SC insulin. Similarly, people with type 2 diabetes have participated in research to determine the efficacy of HIIP as adjunctive therapy to oral anti-diabetic agents and as monotherapy.

Type 1 diabetes research

A 6 month, randomized, multicenter study in patients with type 1 diabetes compared inhaled insulin with SC regular human insulin, both in combination with morning and evening NPH insulin. Results demonstrated similar reductions in A1C levels in both groups although fasting plasma glucose levels fell in the inhaled insulin group compared with an increase in the subcutaneous insulin group. In addition, the inhaled insulin group had better results 2 hours post-prandial than did the SC insulin group. In another 6 month, randomized, multicenter study, patients with type 1 diabetes receiving inhaled insulin and SC ultralente or two to three injections of SC insulin (NPH/RHI), showed similar reductions in A1C, however, fasting plasma glucose levels were significantly lower in the inhaled insulin group. These results are supported by another three month, multi-center trial that showed reductions in A1C levels while the incidence of hypoglycemia was similar for HIIP and SC insulin-treated patients. Another six month, randomized comparative study showed the mean A1C and postprandial glucose decreased in both the inhaled and SC insulin groups.

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Type 2 diabetes research

Research on people with type 2 diabetes is more varied than for people with type 1 diabetes as there are several options for the use of HIIP in this population. Some patients who are struggling to meet their goal with diet and exercise alone may choose to use HIIP as their initial medication. Others who are already taking high or the maximum dosages of oral glycemic agents may integrate HIIP for preprandial use while continuing a longer acting oral medication.

Studies have been done on these varying uses of HIIP. A 12 week randomized comparative study showed that HIIP monotherapy improves glycemic control more quickly than rosiglitazone. A 12 week study investigated the effect of adding HIIP (preprandial) to oral hypoglycemic agents in insulin naïve patients who were poorly controlled solely on oral agents. It demonstrated a greater than two percent decrease in A1C levels in the combination group as compared to the A1C levels of patients on oral agents alone.

Possible Side Effects

The most commonly experienced side effects of HIIP are hypoglycemia and hyperglycemia. People with diabetes may experience both of these side effects at different times relative to the amount of insulin available, carbohydrate intake, and the metabolic demand of the body. Some patients may experience decreased lung function determined by pulmonary function tests (PFTs), however, clinical studies have shown that the pulmonary function changes are non-progressive for up to two years and are reversible upon discontinuation. Serious allergic reaction may manifest as a full body rash, shortness of breath, wheezing, a fast pulse, sweating and low blood sugar. HIIP may cause a cough that has been shown in studies to be mild and decrease over time. Patients who experience bronchospasm need to consult their health
provider immediately. Dry mouth and chest discomfort may also occur. Patients are encouraged to discuss any side effects with their provider.

**Identifying Candidates for HIIP**

HIIP has demonstrated efficacy in both type 1 and type 2 diabetes in its ability to lower A1C and post-prandial plasma glucose measurements. People with type 1 diabetes may be candidates for HIIP, however, they will continue to require at least one subcutaneous injection per day of basal insulin. People with type 2 diabetes have more options for creative inhaled insulin therapy. HIIP may be used as monotherapy in people with type 2 diabetes not adequately controlled with diet and exercise alone as an alternative for people not well controlled with oral therapy or in combination with oral agents. See Table 1 for people who should not use HIIP. Provider discretion should be used in patients taking over the counter medications and herbal supplements to the unknown effect on HIIP absorption and metabolism.

**Table 1:** People who should not use HIIP

<table>
<thead>
<tr>
<th>People that have lung disease or have breathing problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>People using other forms of inhaled medication</td>
</tr>
<tr>
<td>People with decreased liver or kidney function</td>
</tr>
<tr>
<td>Women who are pregnant or plan to become pregnant as there is not enough research to support the safety of HIIP use in these populations.</td>
</tr>
<tr>
<td>Breastfeeding mothers or those who plan to breastfeed due to lack of supporting research.</td>
</tr>
<tr>
<td>People who are smoking or have quit less than 6 months ago</td>
</tr>
</tbody>
</table>

Source: Exubera Medication Guide version 01/272006

**Initiating Therapy**

Providers who anticipate prescribing HIIP must be knowledgeable about the indications, contraindications, and precautions of this innovative therapy. The current Food and Drug Administration approved HIIP comes packaged as a powdered substance in small foil reservoirs called blisters. The blisters come in two different sizes; a 1mg blister that is equal to 3 units of
subcutaneously injected regular human insulin and a 3mg blister which is equal to 8 units of subcutaneously injected regular human insulin. Inhaling multiple 1mg doses will not provide the same response as combinations of 1mg and 3 mg packs because of differences in the percentage of the dose delivered from each blister. Up to 45% of the 1mg blister contents and 25% of the 3mg blister contents may be retained in the blister. The patient should be asked to eat three meals per day. Initial pre-meal doses may be calculated using the following formula: [Body weight (kg) X 0.05mg/kg = pre-meal dose (mg)] rounded down to the nearest whole milligram number (e.g., 3.7 mg rounded down to 3 mg). Initial dosing guidelines for HIIP are listed in Table 2. Additional prescribing guidelines for HIIP can be found in Table 3.

Table 2: Initial dosing guidelines for HIIP

<table>
<thead>
<tr>
<th>Patient weight in kg</th>
<th>Patient weight in lb</th>
<th>Initial dose per meal</th>
<th>Number of 1mg blisters per meal</th>
<th>Number of 3mg blisters per meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to 39.9 kg</td>
<td>66 - 87 lb</td>
<td>1 mg per meal</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>40 to 59.9 kg</td>
<td>88 - 132 lb</td>
<td>2 mg per meal</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>60 to 79.9 kg</td>
<td>133 - 176 lb</td>
<td>3 mg per meal</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>80 to 99.9 kg</td>
<td>177 - 220 lb</td>
<td>4 mg per meal</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>100 to 119.9 kg</td>
<td>221 - 264 lb</td>
<td>5 mg per meal</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>120 to 139.9 kg</td>
<td>265 - 308 lb</td>
<td>6 mg per meal</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 3: Guidelines for HIIP Use.**

HIIP differs from regular human insulin by its rapid onset of action. When used as a mealtime insulin, the dose of HIIP should be given within 10 minutes before a meal. Hypoglycemia is the most commonly reported adverse event of HIIP therapy and the timing of hypoglycemia may differ among various agents. Patients with type 1 diabetes also require a longer-acting insulin to maintain adequate glucose control. Because of the effect of HIIP on pulmonary function, all patients should have a pulmonary function assessment prior to initiating therapy with HIIP.

The use of HIIP in patients with underlying lung disease, such as asthma and COPD, is not recommended because the safety and efficacy of HIIP in this population has not been established. Use of HIIP with respiratory illness such as bronchitis, upper respiratory infection and rhinitis may necessitate closer monitoring of blood glucose concentrations, and dose adjustment may be required.

Patients should be informed that clinical studies of HIIP were associated with small, non-progressive mean declines in pulmonary function. Following initiation of therapy, periodic pulmonary function tests are recommended.


Acessed: February 21, 2007

**Monitoring and Evaluating Effectiveness of HIIP Therapy**

Serum glucose response to HIIP may not be predictable. Patients should monitor their blood glucose often to optimize dosing. There also are additional monitoring parameters beyond blood glucose monitoring. Obtaining baseline PFTs is important as the inhaled insulin has been shown to decrease pulmonary function. Once beginning the inhaled insulin program, PFTs must be checked after six months and then annually. In patients who have a decline of greater than or equal to 20% in FEV1 from baseline, PFTs should be repeated. If the decline in PFTs is confirmed the HIIP should be discontinued. The frequency of A1C testing will depend on the patient’s degree of control. Evaluating the effectiveness is much like that of oral and injectable hypoglycemic agents using home blood glucose monitoring and A1C levels with the exception that PFTs will need to monitored.
Patient teaching

Empowering patients with the knowledge of the diabetes disease process may give them the confidence to be more autonomous in managing their diabetes. Teach patients about all the treatment options and have appropriate literature for them to read.

The HIIP comes with a product information insert that covers the proper use of the inhaler device and technique. Providers should be knowledgeable regarding the inhaler devices and teaching patients to use them correctly. Patients should be instructed to inform their primary care provider of changes in their medication regimens. Patients should be encouraged to develop a consistent meal planning and exercise routine to improve glycemic control. Excessive carbohydrate intake or skipping meals may lead to hyperglycemia or hypoglycemia, respectively. Alcohol can greatly affect blood glucose levels and should be used in moderation or not at all. “Sick day” plans should be formulated and patients should be instructed how to monitor and use insulin differently to accommodate the body’s needs during illness. In addition, providers can give patients the confidence to continue traveling by making a travel needs list, including the necessity of a medic alert bracelet and extra insulin supplies.

Additional Considerations

Research indicates that dosages of HIIP are expected to be much higher than SC insulin due to decreased bioavailability. Two 12-week randomized open label trials indicated that a mean daily prandial HIIP dose for people with type 1 and type 2 diabetes was 12.2mg (equivalent to 36.6 units SC insulin) and 14.6mg (equivalent to 43.8 units SC insulin), respectively. SC insulin doses were only 15.9 and 19.0 units, respectively. Most people will need a combination of the 1mg and 3mg blister packs to attain optimal glycemic control. Each blister is loaded and inhaled individually from the inhalation device and may take more than one
inhalation to get the full dose. Based on dosing guidelines (see Table 2), a 200 pound person will need one 3mg and one 1mg blister for a starting dosage.

Cost of HIIP was predicted to be on average approximately $4 per day, almost three to four times the cost of regular SC insulin assuming three injections a day. Several pharmacies confirmed that the average monthly cost would be approximately $120-150 with a cost of $150 for a “start-up” kit which includes 1mg and 3mg blisters and an inhalation device (B. Moyer, personal communication, February 10, 2007). Patients who are interested in HIIP will ultimately need to discuss the benefits versus extra cost and safety concerns with their provider to determine the best pharmacological option.

Conclusion

Research has demonstrated that providers and patients are often reluctant to begin SC insulin therapy. HIIP may provide NPs’ with an innovative option for patients who need insulin therapy to maximize glycemic control. Not all patients will be good candidates for HIIP. Some may find it too difficult to maintain glycemic control with the less precise blister packs compared to SC insulin. Further research will determine the long-term safety of HIIP as well as the efficacy in the patient populations where it has not been established due to lack of research. For those who may not benefit from HIIP there is continuing research on other non-invasive delivery methods for insulin.
References


