Non-Invasive Insulin-Delivery System: Pulmonary Inhaler

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Diabetes Mellitus (DM) is a chronic disease affecting approximately 6% of the U.S. population. The two main classifications of DM, type 1 and type 2, are characterized by hyperglycemia. Typical symptoms of diabetes include polyuria, polydipsia, and weight loss.

Type 1A DM represents 5% to 10% of patients with DM and generally results from an autoimmune process that destroys the β-cells of the pancreas, leading to insulin deficiency. Type 1B is a rare form of DM in which the cause of the β-cell destruction is unknown. Type 1 DM can develop at any age; however, the incidence generally occurs before age 30 and peaks during puberty.

Type 2 DM accounts for the majority of cases (90%-95%) and represents several metabolic disorders, resulting in varying degrees of insulin resistance, impaired insulin secretion, and increased glucose production. The incidence of type 2 DM increases with advanced age and usually develops after age 45.

There are multiple complications of diabetes, including nephropathy, leading to 40% of newly diagnosed end-stage renal disease cases, peripheral neuropathy leading to amputations, and diabetic retinopathy, which leads to blindness. Other serious repercussions associated with DM are atherosclerotic cardiovascular disease, diabetic ketoacidosis, and hyperosmolar coma.

The Diabetes Control and Complications Trial (DCCT) provided evidence that improved blood glucose control in type 1 DM patients can delay many early complications of the disease and slow the progression of diabetic retinopathy, neuropathy, and nephropathy.

In addition to dietary modifications and exercise, there are multiple medications used in DM. The main treatment of type 1 DM includes two to four subcutaneous injections of insulin daily. Type 2 patients often have the option of oral medications, including sulfonylureas, thienodiolones, biguanides, alpha-glucosidase inhibitors and meglitinide, but many require daily insulin injections as well.

There has been a tremendous amount of research investigating the use of alternative insulin-delivery systems in an effort to alleviate the inconvenience of multiple daily injections in the management of DM. Exubera is one such non-invasive agent in development by Pfizer. It is an investigational agent that introduces a dry powder insulin via a pulmonary inhaler. Currently, phase three trials are being completed, and it is anticipated that Exubera will be submitted to the FDA for approval within the next several months.

**PRODUCT DESCRIPTION**

Exubera is intended to provide reproducible delivery of insulin in an aerosolized form. A powder in discrete foil blister packs contains 1 or 3 mg of recombinant human insulin. The blister pack is opened within the inhaler and a single aerosol cloud is then distributed into a holding chamber. The aerosolized dose is delivered with one inhalation by the patient. The large peptides of insulin are capable of being absorbed into the bloodstream from the alveoli without the use of penetration enhancers.

**PHARMACOKINETICS/BIOAVAILABILITY**

A study was conducted to assess the pharmacokinetics and reproducibility of inhaled insulin (INH) compared to subcutaneous (SC) regular insulin in 16 type 2 non-insulin-treated patients. Study participants underwent a total of five standardized (Sustacal) test-meal sessions: one baseline measurement with no therapy, and then in a four-way, randomized-sequence crossover involving two SC and two INH sessions. INH doses of either four to six inhalations (4-6 mg) or SC insulin doses of 0.2 U/kg were given ten minutes prior to meals. Postprandial hyperglycemia was decreased from baseline (+100±33 mg/dl) by a comparative degree with both INH (to +53±54 mg/dl) and SC insulin (to +57±41 mg/dl). Reproducibility was evaluated based on intra-subject differences between the two same-route dosing sessions. This study concluded that in type 2 patients, postprandial hyperglycemia was similarly reduced with INH with a reproducibility comparable to SC insulin.

Another study evaluated the time-action profile of INH compared to SC Lispro insulin (IL) and regular insulin (RI) utilizing 18 healthy male volunteers (non-smokers, 28±4 years of age, body mass index 24±2 kg/m²) in a three-way crossover study using the euglycemic glucose clamp technique. Following a baseline period of 120 minutes, volunteers either inhaled 6 mg INH, received 18U IL SC or 18U RI SC with subsequent measures of glucose infusion rates over the next 600 minutes. Study results showed that INH had a faster onset of action compared to RI (P=0.001), a duration of action between IL and RI (P=0.0175) and a time to peak effect similar to IL.

Studies have shown that the bioavailability of aerosolized insulin powder without the use of an absorption enhancer is approximately 10%. Cefalu et al. reported, based on data from Pfizer, that pharmacokinetic studies in healthy volunteers indicate that 1 mg of INH supplies the circulation with the approximate equivalent of 3 units of SC insulin without the use of penetration enhancers. Studies show that INH achieves a reproducible effect with an onset of action faster than RI and a relatively long duration of action potentially suitable for supplemental use in patients with DM.

**EFFICACY**

**Type 1 Diabetes**

An open-label, randomized, parallel-group 12-week trial conducted with 73 type 1 DM patients compared the efficacy of INH to conventional SC insulin.
insulin therapy. Patients were placed on a stable insulin regimen involving two to three injections daily for at least two months, and had glycosylated hemoglobin (HbA1c) values between 7% and 11.9%. The experimental group (n=35) took one to two inhalations of INH three times daily before meals, plus SC Ultralente insulin at bedtime. The control group (n=37) continued their pre-study regimen, taking SC insulin two to three times daily.

Inhaled insulin doses were based on blood glucose measurements monitored by participants four times daily, and were adjusted weekly to attain preprandial concentrations between 100 and 160 mg/dl. The primary outcome measure was the change in HbA1c from baseline after 12 weeks. HbA1c values showed no significant difference in response between the two groups. The trial concluded that inhaled insulin provides an equivalent glycemic response over a three-month period, as compared to preprandial SC insulin in type 1 DM patients.

In another three-month trial involving type 1 DM, patients had a pre-study treatment regimen of two to three SC injections of insulin daily for at least two months. Patients were randomized to either their pre-study regimens or to INH prior to meals and SC Ultralente insulin at bedtime. Mean HbA1c levels showed no significant difference between groups (baseline SC=8.53%, INH=8.51%; at three months, SC=7.7%, INH=7.87%).

Type 2 Diabetes
Several trials have been conducted to assess the safety and efficacy of INH in type 2 patients. Cefalu et al. conducted a randomized, open-label, three-month trial with 26 type 2 patients. After a four-week lead-in period, in which patients received their normal SC insulin injections two to three times daily, the patients were randomized to receive INH 10 minutes before each meal, and an injection of Ultralente insulin at bedtime. Glucose monitoring was conducted daily, and insulin doses were adjusted weekly, to attain a targeted preprandial glucose level of 100 to 160 mg/ml. HbA1c and pulmonary function tests (PFTs) were measured at baseline and at 12 weeks. Mean HbA1c levels decreased from 8.67% to 7.96%. Twelve-week change was – 0.71% (95% CI, –1.00% to –0.42%). The authors concluded that INH improved glycemic control.

Another study, conducted on type 2 DM patients who were unable to maintain glycemic control with oral agents (OA), evaluated the benefit of premeal INH added to OA treatments, instead of initiating SC insulin therapy. Sixty-nine patients were enrolled with HbA1c levels over 8% despite doses of glyburide 5 mg per day or more, and/or metformin 1.5 g per day, or more. Subjects were randomized to either continue their previous regimens or to receive the OA plus INH at the rate of one to two puffs three times daily before meals for 12 weeks. Doses were adjusted based on daily glucose testing conducted four times daily. Patients using only OA showed an average HbA1c change of –0.13%, whereas the average HbA1c improvement in the OA + INH group was –2.28% (P<0.0001).

PATIENT SATISFACTION
Cappelleri and colleagues created a 15-item, self-administered questionnaire to evaluate patient satisfaction with INH compared to SC insulin utilizing a five-point Likert scale to analyze each item. Questionnaires were given at baseline and at three months in the Skyler et al. study. Type 1 patient satisfaction was shown to be greater in the INH group compared to the SC therapy with regard to ease of administration, comfort, convenience, and flexibility. Overall, 35% of INH patients reported an increase in satisfaction after three months, compared to 12% of SC patients (P=0.01). However, there was no significant difference in the items representing social stigma (P=0.49). Patients on SC insulin were less self-conscious about taking insulin away from home than those in the INH group.

Of the 72 patients who completed the initial study, 70 decided to remain on the inhaled-insulin regimen in a long-term extension trial. Gerber et al. evaluated the satisfaction in these type 1 patients after a one-year extension trial. Patients were able to choose their insulin regimens (INH or SC) after completion of the three-month randomized trial. At 12 months, global satisfaction was increased in the INH group (38% INH vs. 14% SC) as was convenience/ease of use (46% INH vs. 12% SC). Subjects that remained on the same therapy in both the three-month and 12-month studies maintained their levels of satisfaction. Patients who switched to INH from SC reported a significant improvement (P<0.05) in global satisfaction, convenience/ease of use, and social stigma. By comparison, patients who switched from INH to SC showed a tendency towards decreased satisfaction.

The questionnaire was also utilized to assess patient satisfaction in type 2 DM patients after a 12-week study evaluating INH before meals and Ultralente SC injections at bedtime versus their pre-study regimen of two to three injections daily. Global patient satisfaction was greater (P<0.05) in the INH group (38%) than in the SC group (14%). The items representing convenience, comfort, and ease of use provided greater satisfaction in the INH group than in the SC group (P<0.05).

Testa et al. evaluated satisfaction and quality of life in 334 type 1 patients randomized to either two to three mixed regular/NPH insulin injections per day or preprandial INH plus a bedtime dose of Ultralente injections. In a 24-week trial, questionnaires were completed at baseline, and at 6, 12, 20, and 24 weeks. Patient satisfaction scales included advocacy, burden, convenience, efficacy, flexibility, pain, general satisfaction, hassle, life interference, preference, side effects, and social limitations. All scales showed favorable effects for INH (P<0.0001). The quality-of-life scale, including health perceptions, symptom interference, depression, positive affect, life satisfaction, psychological well-being, and cognitive function showed favorable improvements for INH compared to SC (all P<0.01 to 0.05). There was no difference in INH vs. SC in INH (7.9%) and SC (7.7%) groups.

Simonson et al. evaluated type 2 patients in a randomized trial of oral agents versus inhaled insulin. Patients on a sulfonylurea plus either metformin or a thiazolidinedione were randomized to either current therapy, preprandial INH monotherapy, or current oral agents plus INH. Satisfaction questionnaires were completed at baseline, and at six and 12 weeks. Overall patient satisfaction in the INH group showed no change from baseline to endpoint (P=ns), but was improved in both the INH and the OA + INH groups (P<0.0001 for both).

The subscale evaluating weight gain and hypoglycemia favored OA over OA + INH (P<0.01). A subscale evaluating efficacy favored OA + INH over INH (P<0.05). More favorable satisfaction scores were linked to reductions in HbA1c values. The INH was better in the OA + INH group (7.3%) and the INH group (7.9%) vs. OA (9.1%, P=0.0001). On the whole, OA + INH and INH patients preferred the inhaler to their prior regimen of OA for better glucose control (92%), ease of dose adjustment, overall preference, and feeling better about themselves. However, they preferred OA for use in public because of its convenience, ease of use, and flexibility.

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ADVERSE EFFECTS

The Cefalu et al. study conducted in 26 type 2 DM patients who received inhaled insulin before meals and SC Ultralente insulin at bedtime, reported that 60% of patients experienced mild to moderate hypoglycemia. Hypoglycemia was defined as typical symptoms without glucose measurement, symptoms plus a glucose level below 60 mg/dl, or a glucose level below 50 mg/dl. No severe adverse events and no significant changes in PFTs or body weight were reported. The exact PFT measures utilized in the study were spirometry, lung volume, diffusion capacity, and oxygen saturation.5

The proof-of-concept study9 discussed earlier included non-smoking participants between 18 and 55 years of age, with normal respiratory and cardiac exams and weights between 80% and 130% of ideal body weight. The frequency and severity of hypoglycemia were also evaluated, and changes in pulmonary function were measured. There were no significant differences in occurrences or severity of hypoglycemia between the two groups. Most hypoglycemic events were considered mild to moderate; however, there were eight episodes in the INH group and 10 in the SC insulin group that were considered severe. There were no significant differences in pulmonary function between the groups at the end of the study when compared to baseline.8

One type 1 DM trial reported an average of 5.23 mild-to-moderate hypoglycemia episodes per subject per month in the SC group compared to 5.13 in the INH group, and 10 total severe episodes in the SC group versus eight in the INH group.7 Weiss et al. reported one serious hypoglycemic event with a glucose level of 54 mg/dl in the OA + INH study group. Pulmonary function tests were noted to have no change over the study period of 12 weeks.10

LONG-TERM EFFICACY/SAFETY

All subjects who had completed any of three 12-week randomized phase II trials were invited to remain on INH in long-term extension trials of up to two years to evaluate its long-term pulmonary safety and efficacy. Over 100 type 1 and type 2 DM patients participated. Efficacy was maintained throughout the two-year period and was supported by stable HbA1c levels (baseline=8.9%, end of three-month trial=8.0%, at 24 months=8.0%). In addition, forced expiratory volume in one second was unchanged (baseline=3.2, 24 months=3.2), and diffusion capacity was also relatively stable (baseline=25.6, 24 months=24.4) in this patient population.17

Concerns have been raised regarding the vasodilating and pro-inflammatory effects of insulin in the pulmonary vasculature. Patients with pulmonary or cardiac disorders might require careful monitoring or might not even be candidates for treatment until further studies in these populations are conducted.10,11

DOSAGE AND ADMINISTRATION

The Cefalu et al. study utilized doses of one to two inhalations of insulin per meal for an average of 14.6 mg of inhaled insulin per day.2 Data cited in this study indicated that in healthy volunteers, 1 mg of INH is equivalent to approximately 3 units of SC insulin. Therefore, initial doses are suggested at 3, 6, 9, 12, or 18 units with subsequent titrations based on individual responses.5

CONCLUSION

Maintaining glycemic control in a reproducible manner is an essential component of any diabetes treatment regimen. Although there are various pharmacological options available to treat type 2 patients today, all type 1 patients and many type 2 patients require subcutaneous injections of insulin for treatment. Numerous individuals resist the daily use of multiple subcutaneous injections, thereby decreasing adherence and subsequent glucose control. Such patients are likely candidates for INH therapy because of its increased convenience and ease of use, as evidenced by the results of patient-satisfaction questionnaires.

It has been shown that large doses of INH are required to attain blood concentrations equivalent to those obtained with SC therapies. Although absorption enhancers would increase the bioavailability of INH, thereby allowing for smaller doses of aerosolized insulin, the lack of such penetration enhancers in Exubera decreases the potential risk of additional safety concerns and adverse reactions.4

Although preliminary data suggest that inhaled insulin has no adverse effects on pulmonary function tests, it is difficult to extrapolate from this information and apply it to all patients with diabetes based on the exclusion criteria used in most studies. Patients were excluded from the trials if they had a major organ system disease (except hypertension and complications directly related to diabetes) or if they had been smokers within the past six months.5,8

A two-year extension trial is not adequate to assess the safety of inhaled insulin. Long-term studies are needed to evaluate the efficacy and pulmonary safety for all patients with diabetes. Until the results from such studies are published, one is unable to fully elucidate the effectiveness of inhaled insulin in these patient populations.

Overall, studies have shown that inhaled insulin provides a reproducible glycemic effect in type 1 and type 2 DM patients; a fast onset of action; a duration of action between Lispro and regular insulin;7 and an agreeable drug profile in non-smoking patients with no pulmonary or cardiac dysfunctions.5,8 When combined with bedtime Ultralente SC, preprandial INH appears to provide glycemic control comparable to SC insulin, thereby providing a non-invasive alternative for select DM patients.

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