Inhaled Insulin—A New Insulin Delivery System

a report by

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The inhaled insulin, Exubera®, was recently approved for the treatment of type 1 and type 2 diabetes. This article will review the delivery systems for inhaled insulin, the kinetics of inhaled insulin, clinical trials in type 1 and type 2 diabetes, and safety considerations for inhaled insulin.

Delivery of Inhaled Insulin

The lungs are an excellent target for the delivery of medications since the lungs have a highly permeable membrane, a large surface area ($140m^2$ in adults), and a rich blood supply.[1,2] Several factors affect where inhaled particles will be deposited in the respiratory system such as the size, solubility, and velocity of the particle. The new insulin delivery systems that have either been approved for clinical use or are in clinical trials use either a dry powder or a liquid formulation of insulin.[3,4] The insulin can be administered to the lungs by an aqueous mist inhaler or a dry powder inhaler. Insulin delivery systems which are under investigation include Exubera (Pfizer, Nektar), AERx iDMS (Novo-Nordisk), Technosphere (Mannkind), and AIR (Eli Lilly, Alkermes). The device used for the delivery of Exubera uses a dry powder insulin, which contains insulin (60%), mannitol, sodium citrate, and glycine. The insulin is packaged into 1mg or 3mg blisters, which contain approximately the equivalent of three or nine units of insulin. The blister is placed into the inhaler and, utilizing compressed air, the insulin is aerosolized into a transparent holding chamber. The patient views a cloud of aerosolized insulin, and during the beginning of a deep breath, the patient inhales the insulin through a mouthpiece.

Pharmacokinetics

Inhaled insulin has pharmacokinetic properties similar to the rapid acting insulin analogs and hence is used for premeal insulin coverage. The properties of inhaled insulin (Exubera 6mg), lispro insulin (18 units), and regular insulin (18 units) were determined in a euglycemic clamp study in 17 healthy male volunteers.[5] The onset of action (time to reach 50% maximal glucose infusion rate) was shorter for Exubera (32 minutes) compared to lispro and regular (41 minutes, $p<0.05$ and 48 minutes, $p<0.001$, respectively). The time to maximal effect was similar for inhaled insulin (143 minutes) and lispro (137 minutes), but it was shorter compared to regular (193 minutes, $p<0.01$). The duration of action (time to reach late half maximal effect) was similar for inhaled insulin (387 minutes) and regular (415 minutes), but it was longer than lispro (313 minutes, $p<0.01$).

A similar study measured the dose response of lispro insulin and inhaled insulin delivered by the AIR particle technology.[6] Different dosages of inhaled insulin (2.6, 3.6, 5.2, or 7.8mg) and lispro insulin (6, 12, or 18 units) were studied, and the study found that

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the relative bioavailability of inhaled insulin was consistent across different doses. Similar findings regarding the pharmacokinetics of inhaled insulin have been reported in subjects with type 1 and type 2 diabetes.[7,8] The absorption of inhaled insulin is increased in smokers compared to nonsmokers,[9,10] and patients with asthma absorb less insulin compared to healthy volunteers.[11]

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Clinical Trials: Type I DM

Several clinical studies in type 1 diabetes have evaluated the efficacy and tolerability of inhaled insulin.[12] These studies have shown that inhaled insulin and subcutaneous insulin can achieve similar glycemic control.[13] In a six-month study, 335 type 1 diabetics were randomized to prandial inhaled insulin and ultralente or regular and NPH insulin.[14] The decrease in the HbA_{1c} was similar for inhaled insulin (8.1% to 7.9%) and subcutaneous insulin (8.1% to 7.7%; adjusted treatment group difference 0.16%, 95% CI -0.01 to 0.32).

In a second six-month study, 328 type 1 diabetics were randomized to prandial inhaled insulin and twice daily NPH or regular insulin and twice daily NPH.[15] The decrease in HbA_{1c} was similar for inhaled insulin (8.0–7.7%) and subcutaneous insulin (7.9–7.8%; adjusted treatment group difference -0.16%, CI -0.34

to -0.01). In both studies, larger reductions in the fasting plasma glucose were observed in inhaled insulin group. For instance, in the second study, the mean adjusted change in the fasting plasma glucose was -35mg/dl in the inhaled insulin group compared to +4mg/dl in the subcutaneous group (treatment group difference -39.5 mg/dl, CI -57.5 to -21.6). In both studies, the risk for hypoglycemia was slightly lower for inhaled insulin compared to subcutaneous insulin. However, in the second study, the risk for severe hypoglycemia was higher in the inhaled insulin group (6.5 versus 3.3 events per 100 patient–months; risk ratio 2.00, CI 1.28 to 3.12).

An open-label crossover study compared inhaled insulin and subcutaneous insulin (lispro or regular) in 137 type 1 diabetics on glargine.[16] Patients were given inhaled insulin and glargine for 12 weeks, followed by subcutaneous insulin and glargine for 12 weeks. The treatment order was reversed for some of the patients. There were no significant differences in the HbA_{1c} between the inhaled insulin and subcutaneous insulin groups, and the rate of hypoglycemia was similar between the two groups. However, the fasting blood glucose was lower in the inhaled insulin group, and the rate of nocturnal hypoglycemia was higher in the inhaled insulin group (4.2 versus 2.7 events per 30 days, p<0.001).

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Clinical Trials—Type 2 DM

Clinical trials with inhaled insulin have been conducted in subjects with type 2 diabetes previously treated with diet, oral agents, or insulin. In a three-month study, 145 type 2 diabetics suboptimally controlled on diet (HbA_{1c} 8–11%) were randomized to inhaled insulin or rosiglitazone, 4mg twice a day.[17] The decrease in the HbA_{1c} was greater for inhaled insulin compared with rosiglitazone (-2.3% versus -1.4%; adjusted treatment group difference -0.89%, 95% CI -1.23 to -0.55). Of note, 44% of patients in the inhaled insulin group achieved a HbA_{1c} less than 7.0% compared with 18% of the patients in the rosiglitazone group (odds ratio 4.43, 95% CI 1.94 to 10.12).

significant improvement in the HbA_{1c} in the patients treated with inhaled insulin (-1.9% for insulin plus two oral agents, -1.4% for inhaled insulin alone, -0.2% for two oral agents). A HbA_{1c} of less then 7% was achieved in 32% of the patients on inhaled insulin and two oral agents (odds ratio 44.7, CI 6.0 to 335.2), 16.7% of the patients on inhaled insulin alone (odds ratio 19.0, CI 2.5 to 145.8), and 1% of the patients on oral agents alone.

The use of inhaled insulin versus subcutaneous insulin has also been evaluated in type 2 diabetics. In a six-month trial, type 2 diabetics were randomized to inhaled insulin and ultralente or to subcutaneous regular and NPH insulin.[20] The decrease in the hemoglobin HbA_{1c} was similar between the inhaled insulin and subcutaneous insulin

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Inhaled insulin can improve glycemic control in type 2 diabetics suboptimally controlled on oral agents. In a six-month study, inhaled insulin and metformin were compared in 427 poorly controlled type 2 diabetics on a sulfonylurea.[18] In the subset of patients with an initial HbA_{1c} greater than 9.5%, the decrease in HbA_{1c} from baseline was greater for inhaled insulin compared with metformin (-2.17% versus -1.79%; adjusted difference -0.38%, 95% CI -0.63 to -0.14). However, in the subset of patients with an initial HbA_{1c} from 8% to 9.5%, the change in HbA_{1c} was similar for inhaled insulin and metformin. Another three-month study evaluated 309 type 2 diabetics (HbA_{1c} 8–11%) on two oral agents (a sensitizer and secretagogue).[19] The patients were divided into three groups—inhaled insulin alone, inhaled insulin and two oral agents, or oral agents alone. There was a

groups (-0.7% versus -0.6%, adjusted difference -0.07%, 95% CI -0.32–0.17). Hypoglycemic events were lower in the group treated with inhaled insulin (1.4 versus 1.6 events per patient month; risk ratio 0.89, 95% CI 0.82–0.97).

Safety—Pulmonary Function and Insulin Antibodies

In all studies, patient satisfaction is greater in patients receiving inhaled insulin when compared to subcutaneous insulin.[21-23] In patients with type 2 diabetes, the availability of inhaled insulin allows for greater acceptance of insulin therapy.[24] However, there are two main safety considerations regarding the use of inhaled insulin—the effects on pulmonary function and the development of insulin antibodies.[25]

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Cough is more common with inhaled insulin therapy (27% versus 5%).[14] Some studies suggest a small but nonprogressive decline in pulmonary function in patients treated with inhaled insulin.[14,20,27-28] In a six-month study in type 1 diabetics, a decrease in DL_{CO} was noted in the inhaled insulin group.[14] However, in a similar six-month study in type 2 diabetics, no significant differences in pulmonary function tests were noted in the inhaled insulin group.[20] In a two-year study in type 2 diabetics receiving inhaled insulin or a second oral agent, the change in FEV_1 from baseline was greater in the inhaled insulin group at 24 weeks.[27] However, this difference did not increase at 52 or 104 weeks. The differences in the DL_{CO} were small between the two groups. Twelve weeks after

Several studies have shown that the prevalence of insulin antibodies is higher in patients receiving inhaled insulin.[14-15,18-20] In a study of 47 patients with type 1 diabetes, the development of insulin antibodies did not affect the clinical safety or the pharmacodynamics of inhaled insulin.[29] An analysis of several phase II and III clinical trials revealed that patients given inhaled insulin developed a larger antibody response than patients given subcutaneous insulin, and the antibody response was largest for patients with type 1 diabetes.[30] Peak insulin antibody levels developed six to 12 months after exposure. The antibody response is non-neutralizing and predominantly of the IgG type. The presence of antibodies was not associated with changes in glycemic control, changes in insulin doses, hypoglycemic events,

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discontinuing therapy, there were no significant differences in the FEV_1 or DL_{CO} between the two groups. In an extension study, pulmonary function studies were determined in 89 patients who completed four years of inhaled insulin therapy.[28] In the patients receiving inhaled insulin, the annualized change in the FEV_1 (mean +/- SE) was -0.057 +/- 0.004 L/yr, and the annualized change in the DLCO was -0.376 +/- 0.067mL/min/mmHg/yr. In patients not receiving inhaled insulin (two-year data, n=23), the annualized change in the FEV_1 was -0.071 +/- 0.023 L/yr, and the annualized change in the DL_{CO} was -0.673 +/- 0.423mL/min/mmHg/yr. Hence, pulmonary function tests should be obtained at baseline, at six months after starting insulin therapy, and annually thereafter.[26]

changes in pulmonary function tests, or the incidence of hypersensitivity reactions.

Conclusions

Several clinical trials in type 1 and type 2 diabetics have demonstrated the efficacy and safety of inhaled insulin, and shown that inhaled insulin and subcutaneous insulin can achieve similar glycemic control. Studies that have examined the side effects of inhaled insulin have shown that inhaled insulin is well tolerated, and its use is associated with increased patient satisfaction. Given the efficacy and tolerability of inhaled insulin, inhaled insulin is a promising new delivery system that provides prandial insulin coverage, and it may ultimately play an important role in the future management of diabetes. ■

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