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AERx® iDMS

Treatment of Type 1 and Type 2 Diabetes

AERx® Insulin Diabetes Management System
NN-1998

Aerosol pulmonary delivery system of liquid human insulin formulation using AERx® insulin diabetes management system

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Abstract

The standard form of insulin therapy for the treatment of diabetes is via subcutaneous injection. However, this method of delivery is associated with a reduction in patient compliance and does not mimic the physiological patterns of insulin secretion. As a result, blood glucose and other metabolic parameters cannot be maintained at normal levels. The introduction of rapid- and long-acting insulin analogues has resulted in improved glycemic control, although multiple daily injections are generally required. Alternative routes of insulin delivery have been studied with limited success. Recently, special attention has been given to the pulmonary route of delivery, which has many advantages over other routes and could decrease the number of daily insulin injections, resulting in improved compliance and optimal long-term glycemic control. Of the inhaled insulins under development, the AERx® insulin Diabetes Management System (AERx® iDMS) has shown particular promise. The system involves the delivery of a liquid form of human insulin using a unique breath guidance system that enables patients to breathe optimally and reproducibly. The resulting pharmacokinetic profile of insulin resembles that of short-acting insulin analogues, indicating that inhaled insulin can be given immediately before a meal. The bioavailability of insulin following the use of AERx® iDMS was 13-17% and the system was shown to be effective, safe and well tolerated in a number of clinical studies. AERx® iDMS has reached phase II development for the treatment of type 1 and 2 diabetes.

Introduction

Diabetes is currently the fourth leading cause of death in most developed countries. The World Health Organization (WHO) estimates that there over 177 million people worldwide with diabetes, and by the year 2025, there will be 300 million people suffering from the disease. According to the American Diabetes Association, 18.2 million Americans have diabetes, of whom only two-thirds are diagnosed, and there are almost 1 million new cases of diabetes diagnosed each year in the U.S. among individuals aged 20 years or older (1, 2).

Insulin was discovered in 1921 and entered clinical practice in 1922. It remains the mainstay of therapy for type 1 diabetes and is eventually required in nearly half of all patients with type 2 diabetes. Administration of insulin in the form of bolus subcutaneous injections is the standard form of therapy. However, this method of dosing does not result in replication of physiological patterns of insulin secretion and it is therefore nearly impossible to maintain blood glucose and other metabolic parameters at normal levels. The introduction of regimens including both rapid- and long-acting insulin analogues has resulted in improved glycemic control. However, these regimens are complex, involving multiple daily injections or continuous insulin infusion, which can significantly reduce patient compliance and thus compromise glycemic control (1, 3).

Since the introduction of insulin therapy, researchers have attempted to develop alternative routes of delivery for insulin, such as transdermal, nasal, rectal, ocular, buccal, vaginal and uterine, but have had limited success. Recently, special attention has been given to the pulmonary route, which has been used successfully for many years for the treatment of asthma and other respiratory diseases. The pulmonary route of administration has many advantages, including fast onset of action and improved systemic absorption of drugs such as peptides due to the large surface area provided by the lungs as compared to oral, rectal, nasal and vaginal cavities. Moreover, excellent advances have been made in the development of inhaler devices. Pulmonary administration could decrease the number of daily insulin injections required and therefore result in improved compliance and optimal long-term glycemic control (1, 4-8).

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Several inhaled insulins are currently under development, including both liquid and dry powder formulations (1, 9, 10) (Table I). The AERx® Insulin Diabetes Management System (AERx® iDMS) is a particularly promising drug/device system that involves the delivery of a liquid form of human insulin using a unique breath guidance system which enables patients to breathe optimally and reproducibly. The drug is delivered as a fine-droplet aerosol and is not delivered if breathing is not correct. In addition, the system uses strips with liquid insulin that facilitate dose adjustments which are comparable to those with insulin injections, and includes an electronic monitoring device which can provide important information about dosing regimens and compliance. AERx® iDMS was therefore chosen for further development for the treatment of type 1 and 2 diabetes (1, 10).

Table I: Inhaled insulins currently under active development (from Prous Science Integrity®).

Drug	Source	Phase
Exubera®	Pfizer; Sanofi-Aventis; Nektar Therapeutics	Prereg.
AIR® Insulin	Alkermes; Lilly	III
AERx® iDMS	Novo Nordisk; Aradigm	II
KI-02212	Kos Pharmaceuticals	II

Pharmacokinetics

Results from an open-label, randomized, crossover study in 21 healthy subjects showed that breath-holding (3 or 10 s) following a single inhalation of regular human insulin (45 IU) using AERx® iDMS did not alter any pharmacokinetic or pharmacodynamic parameter. Mean serum insulin $AUC_{0\text{-}360\ min}$ values were 8218, 8244 and 8404 μU/ml·min for postdosing breath-holding durations of 0, 3 and 10 s, respectively. Mean insulin C_{max} values were 44.9, 44.2 and 45.5 μM/ml respectively, and mean plasma glucose area over the curve ($AOC_{0\text{-}360\ min}$) values were 3512, 4033 and 3708 mg/dl·min, respectively. It was concluded that breath-holding may not be required following insulin inhalation using AERx® iDMS (11).

An open-label, parallel-group study compared insulin pharmacokinetics and pharmacodynamics in 28 healthy and 17 asthmatic (forced expiratory volume in 1 s [FEV_1] = 50-80% of predicted value) subjects following a single inhalation of insulin (45 IU on day 1 and 135 IU on day 2 to assess pulmonary function) using AERx® iDMS. Results demonstrated that the amount of absorbed insulin was significantly decreased in asthmatic subjects as compared to healthy subjects (insulin $AUC_{0\text{-}360\ min}$ = 1.45 x 10^6 and 1.07 x 10^6 pmol/l·min·kg, respectively). Healthy subjects had a significantly greater reduction in serum glucose compared to asthmatic subjects ($AOC_{0\text{-}360\ min}$ = 4880 and 3419 mg/dl·min, respectively). The insulin C_{max} values for both groups were not significantly different (9872 and 8310 pmol/l·kg, respectively) and no significant changes in FEV_1, forced vital capacity (FVC) and FEV_1/FVC were seen. Inhalation of insulin using AERx® iDMS was well tolerated in both groups. Adverse events were mild, transient and self-limited, the most frequent being hypoglycemia, headache and dizziness. No relevant changes were observed in blood pressure, heart rate, ECG or laboratory parameters. It was concluded that diabetic patients with asthma may require a higher dose of inhaled insulin compared to diabetics with normal respiratory function (12).

The pharmacokinetics and intrasubject variability of single doses of inhaled insulin (33.8 IU) using AERx® iDMS were examined in 27 healthy smokers and 16 healthy nonsmokers, with results showing that total insulin absorption was significantly greater in smokers ($AUC_{0\text{-}6\ h}$ = 40 mU/l·h *vs*. 63.2 mU/l·h; C_{max} = 13.9 mU/l *vs*. 42 mU/l; t_{max} = 53.9 min *vs*. 31.5 min). The intrasubject variability of $AUC_{0\text{-}6\ h}$ was low (16.5% and 13.7%, respectively, in smokers and nonsmokers) as compared to previously reported results for s.c. insulin. There were only a few mild adverse events reported and no relevant changes in pulmonary function, vital signs or laboratory parameters (13).

Results from an open-label, crossover study in 20 otherwise healthy adult subjects showed that there were no differences in insulin (45 IU) pharmacokinetics during acute uncomplicated upper respiratory tract infection (URTI) and following recovery (within 3 weeks of the first dose) using AERx® iDMS. Inhaled insulin using AERx® iDMS was well tolerated and not associated with relevant changes in pulmonary function. It was concluded that insulin dose adjustments using AERx® iDMS would most likely not be required in diabetic patients with an acute URTI (14).

An open-label, parallel-group study compared the pharmacokinetics and pharmacodynamics of a single inhalation of regular human insulin (45 IU on 2 days) using AERx® iDMS in 27 young (18-45 years) and 28 elderly (65 years or older) patients with type 2 diabetes. Inhaled insulin using AERx® iDMS was well tolerated, with no relevant changes in pulmonary function reported. Analysis of data from 50 subjects revealed that the $AUC_{0\text{-}360\ min}$ and C_{max} for insulin and intrasubject variability were similar for elderly and young subjects. In contrast, elderly subjects had a significantly smaller reduction in glucose ($AOC_{0\text{-}360\ min}$ = 12,272 ± 6837 mg/dl·min *vs.* 16,337 ± 7142 mg/dl·min). It was concluded that elderly patients with type 2 diabetes may need to inhale a higher dose of insulin when using AERx® iDMS as compared to younger patients. However, long-term studies are required to further determine the significance of the age-related differences seen with AERx® iDMS (15).

A randomized study in 15 nonsmoking subjects with type 1 diabetes compared the onset of action of inhaled insulin using AERx® iDMS, s.c. regular human insulin and s.c. insulin aspart (0.3 IU/kg). The onset of action of inhaled insulin was significantly faster than s.c. regular human insulin (time to 10% of $AUC_{GIR(0\text{-}10\ h)}$ = 72 min *vs.* 89 min) but similar to s.c. insulin aspart (66 min). In addi-

tion, the duration of action of inhaled insulin was longer than insulin aspart (time interval from time to 10% of $AUC_{GIR(0\text{-}10\ h)}$ to time to 90% of $AUC_{GIR(0\text{-}10\ h)}$ = 291 min *vs.* 209 min) but similar to regular human insulin (297 min). Adverse events were infrequent and mild and no safety issues were reported. These results suggest that inhaled insulin using AERx® iDMS can be administered at mealtime (16). The results from this and the following clinical pharmacokinetic/clinical studies are shown in Table II.

An open-label, crossover trial in 21 subjects with type 1 diabetes compared the pharmacodynamic and pharmacokinetic dose-response profiles of inhaled insulin using AERx® iDMS (0.15, 0.64, 1.12 and 1.61 U/kg) and s.c. human insulin (0.03, 0.13 and 0.23 U/kg). The pharmacokinetics of both inhaled and s.c. insulin were linear. $AUC_{0\text{-}10\ h}$ values for the doses of s.c. insulin were in the same range as those for inhaled insulin. The t_{max} for s.c. insulin was dose-dependent, whereas it did not change with inhaled insulin. These results suggest that insulin inhaled using AERx® iDMS can be administered during mealtime. Pharmacodynamic dose linearity according to $AOC_{0\text{-}10\ h}$ values was observed for both inhaled and s.c. insulin. No drug-related adverse events were reported (17).

Comparable intrasubject variability was obtained for inhaled human insulin using AERx® iDMS and s.c. human insulin in a randomized, open-label, parallel trial conducted in 17 nonsmoking patients with type 1 diabetes. No significant differences in intrasubject variability were observed between treatment groups for insulin $AUC_{0\text{-}6\ h}$ and glucose $AUC_{0\text{-}6\ h}$ values. The intrasubject variability for insulin half-life, terminal elimination rate constant and mean residence time was significantly lower in the group receiving inhaled insulin. Inhaled insulin was well tolerated, with no relevant changes in lung function, and only 1 possibly drug-related adverse event was reported (development of an audible wheeze). It was concluded that insulin can be reproducibly administered using AERx® iDMS (18).

Clinical Studies

The safety and efficacy of inhaled insulin using AERx® iDMS (2 inhalations immediately before consumption of a Sustacal® meal) and s.c. regular insulin (8 U 30 min before Sustacal®) were shown to be comparable in an open-label, randomized, crossover study conducted in 20

Table II: Clinical/clinical pharmacokinetic studies of AERx® iDMS (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Diabetes, type 1	Randomized Open Crossover	Inhaled insulin, 0.3 U/kg inhal. Insulin aspart, 0.3 U/kg s.c. Human insulin, 0.3 U/kg s.c.	15	Onset of action of inhaled insulin was similar to that of subcutaneous insulin aspart and significantly faster than that of subcutaneous regular human insulin in patients with type 1 diabetes	16
Diabetes, type 1	Randomized Open Crossover	Inhaled insulin, 0.15 U/kg inhal. Inhaled insulin, 0.64 U/kg inhal. Inhaled insulin, 1.12 U/kg inhal. Inhaled insulin, 1.61 U/kg inhal. Human insulin, 0.03 U/kg s.c. Human insulin, 0.13 U/kg s.c. Human insulin, 0.23 U/kg s.c.	21	Human insulin was safe and time to maximum insulin concentration increased dose-dependently after subcutaneous, but not inhaled, insulin in patients with type 1 diabetes	17
Diabetes, type 1	Randomized Open	Inhaled insulin [before breakfast] I x 4 d (n=9) Insulin s.c. [before breakfast] x 4 d (n=8)	17	The intrasubject variability of insulin and glucose profiles for inhaled insulin was similar or lower compared to subcutaneous insulin in patients with type 1 diabetes	18
Diabetes, type 1	Randomized Open Crossover	Inhaled insulin x 2 [immediately before meal] Insulin, 8 U s.c. [30 min before meal]	20	Glucose profiles were similar after administration of inhaled and subcutaneous insulin followed by ingestion of a standard meal in patients with type 1 diabetes	19
Diabetes, type 2	Randomized Open Multicenter	Inhaled insulin + NPH insulin o.d. x 12 wks (n=54) Human insulin s.c. + NPH insulin o.d. x 12 wks (n=53)	107	Inhaled insulin combined with NPH insulin was as effective as subcutaneous insulin combined with NPH insulin in reducing plasma glucose levels in patients with type 2 diabetes. Neither combination therapy had any adverse effect on lung function after 12 weeks of treatment. An interim analysis conducted in 32 patients who had received inhaled insulin for an average of 83 days revealed that this inhaled insulin system was associated with a high compliance rate. Twenty-five patients took at least 90% of the doses and achieved a mean reduction of 0.53% in the levels of HbA1c	20-22

patients with type 1 diabetes. No changes in pulmonary function were observed with AERx® iDMS. Results from 15 evaluable patients showed that there was no significant difference in glucose concentrations at 60, 120 and 300 min postmeal (19).

A 12-week, multicenter, randomized, open-label, parallel trial in 107 nonsmoking patients with type 2 diabetes showed that fast-acting inhaled insulin using AERx®iDMS given immediately before meals was as effective as s.c. fast-acting insulin given 30 min before meals in achieving glycemic control. Both treatment groups received NPH insulin at bedtime and insulin doses were based on each patient's previous insulin requirements. Adverse events were infrequent, mild and similar for both treatment groups. Results from pulmonary function tests performed at inclusion and after 12 weeks of treatment revealed that there was no significant change in lung function in either group. HbA1c levels were not significantly different between the inhaled and s.c. insulin groups after 12 weeks of treatment (7.84 ± 0.77% and 7.76 ± 0.77%, respectively). The group receiving inhaled insulin had significantly lower fasting serum glucose at the end of the treatment period as compared to the s.c. insulin group (8.9 ± 3.8 mmol/l *vs.* 10.8 ± 3.7 mmol/l) even though the NPH insulin doses were not significantly different between groups. No significant differences in intrasubject variability in fasting or prandial blood glucose increments were observed between groups (20, 21). Analysis of 46 of the 107 patients involved in the above study revealed an excellent compliance rate with mealtime dosing of inhaled insulin using AERx® iDMS. The mean compliance rate was 93.8 ± 12.3% and the mean percentage of missed doses was 4.4 ± 17.3% (excluding outliers). Of these 46 patients, 44 took more than 80% of the prescribed doses. The mean daily insulin dose was 31.5 ± 12 U. Those patients who had a compliance rate of 90% or greater (n=39) and 95% or greater (n=6) experienced a mean reduction in HbA1c levels of 0.77 ± 1.01% and 2% or more, respectively. One patient with the poorest compliance rate (22%) experienced an increase in HbA1c of 0.6%. Poor inhalation technique was observed in only a few patients (22).

AERx® iDMS is presently undergoing phase II development for the management of type 1 and 2 diabetes (23).

Sources

Aradigm Corp. (US); licensed to Novo Nordisk A/S (DK).

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