Recent Trends in Insulin Delivery by Means of Technosphere Drug Delivery Mechanism: A Review

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***Abstract*— Technosphere/Insulin [TI] is formulation of regular human insulin designed for efficient transport across respiratory epithelium into the circulation. The drug carrier mechanism achieves a fast systemic insulin uptake (maximum time 15-20 min.), a fast onset of action (maximum activity 25-30 min.) and short duration of action (2 h). Bioavailability relative to subcutaneous injection was established to be between 30 and 50% with a linear dose response relationship and low variability. In all published short-term study, TI was well tolerated. Provided a reliable long term safety profile, TI may become a suitable alternative to subcutaneous injection for prandial insulin delivery. TI offers the possibility of new treatment regimens, especially in patient with type 2 diabetes.**

***Index Terms*— diabetes mellitus, inhalation, pulmonary insulin, technosphere**

I. INTRODUCTION

Subcutaneous injection is today the only approved effective way for administering insulin in daily clinical routine. The beneficial effect of multiple daily injection regimens has been clearly demonstrated in landmark studies such as the Diabetes Control and Complications Trial [1], And even the United Kingdom Prevention of Diabetes Study provides evidence of the positive impact of improved glycaemic control on the prognosis of Type 2 diabetic patients, despite major design problems [2]. Patients with Type 2 diabetes commonly undervalue the role of lifestyle changes and pharmacological therapy in preventing future complications. Negative emotions and preconceptions about treatment can also discourage adherence to treatment plans. Psychological insulin resistance caused by fear and concerns about insulin and daily insulin injections can discourage many patients from starting insulin therapy, even if oral agents have failed [3,4].

As a consequence, many different routes of application have been investigated since the discovery of insulin > 80 years ago, including oral, rectal, intrascrotal, sublingual, ocular, vaginal, pulmonary, tracheal, transdermal and intranasal approaches [5]. Although some companies and research groups are seriously working on oral insulin delivery, so far only the pulmonary route of administration can be seriously considered to become a suitable alternative to subcutaneous injections. The lung, with its vast and well-perfused absorptive surface, its thin alveolar–capillary barrier, a marginal variance in the amount of mucus production and the absence of an immediate insulin degradation by the liver, has some inherent advantages for insulin administration as given in **Table 1** [6-8]. Currently, several inhaled insulin formulations are being tested in Phase II – III clinical trials, as discussed in Section, and a variety of well-controlled studies have been published in recent years. Some of the pulmonary insulin developments use liquid insulin, whereas others administer dry powder formulations with different inhaler technologies of varying complexities to achieve the optimal particle size of 1 – 3 μm for delivery to the alveoli in the deep lung [9]. However, dry powder formulation seems to have some favourable advantages, such as (but not limited To) stability at room temperature, stability of particle size or low susceptibility to microbacterial growth [10]. Another advantage of pulmonary insulin delivery seems to be improvements in the pharmacokinetic and pharmacodynamic profiles leading to a faster onset and shorter duration of action, which improves the overall reliability and convenience for postprandial glucose control, by achieving insulin concentrations close to, or identical with, short-acting insulin analogues [11,12]. A comparison between liquid and dry powder

formulations is provided in Table 2. Today, the largest body of clinical data is published for the most advanced product Exubera® (Pfizer/Nektar), a dry powder development that was filed for approval in Europe in February 2004 and for the new drug application in the US in December 2004. All other pulmonary insulin developments will have to continue for several years before regulatory filing may be achieved. Objections and regulatory challenges to be addressed during the regulatory development of pulmonary insulin include questions of pulmonary function impairment over long-term use as indicated by a loss in carbon monoxide diffusion capacity, and an increased immunogenicity leading to substantially higher antibody levels as compared with subcutaneous insulin injections [13]. However, recent publications and presentations at the large conferences seem to provide evidence of an acceptable safety and tolerability profile, at least for the Exubera technology [14-17]. Despite an increasing knowledge about the interaction of insulin with the lung tissue, open questions still concern the long-term impact of pulmonary insulin delivery on pulmonary function. Other unmet needs that require further investigation include insulin deposition into the respiratory tract after inhalation and also more practical issues, such as inhaler size, practicability of the inhalation procedure, and economic and reimbursement issues, as the low relative bioavailability of 10 – 20% (measured over 6 h) of most of the pulmonary developments may require a higher price of the final end product. Some of these challenges may be met by Technosphere ™/Insulin (TI), a pulmonary insulin formulation that provides the further focus of this article.

Table no. I. Advantages for pulmonary versus injectable insulin

Parameter	Injectable insulin	Pulmonary insulin
Patient-related factors;		
Psychological barriers	High	Low
Pain	Pain is dependent on the injection devices used	No pain
Acceptance for multiple applications	Low	High
Stigmatization	Drug abuser	None
Technical parameters;		
Absorption surface area	Small region in subcutaneous tissue	Large pulmonary surface
Pharmacokinetic	Variable and relatively slow absorption, changes in pharmacokinetic requires changes in insulin chemistry	Fast absorption, lower variability, similar to sub cutaneous changes in pharmacokinetic can be obtained by mechanism modulating pulmonary absorption
Storage conditions	Unstable, Cooling required (4 – 8°C) No freezing	Relatively stable, room temperature, freezing possible

Table no. II: Differences between liquid and dry powder formulations for pulmonary insulin delivery

Parameter	Pulmonary insulin formulations	
	Liquid	Dry powder
Bioavailability (compared with subcutaneous injections)	15 – 20%	10 – 50%
Tmax	40 – 50 min	15 – 60 min
Stability	Similar to subcutaneous insulin formulations	Stable at room temperature Freezing possible
Dosing (in subcutaneous equivalents)	1 IU	3 IU
External energy (battery) requirements for deagglomeration	High	None or low
Risk for micro bacterial growt	Substantial	Low

II. CHEMISTRY AND FORMULATION:

Technosphere is a drug delivery system made up of microparticles of fumaryl diketopiperazine (FDKP) which forms microspheres (2–5μm) via hydrogen bonds in a mildly acidic medium sufficient for inhalation. During the precipitation process that is used to form microspheres in solution, peptides and proteins are introduced into the solution, which are then microencapsulated within the FDKP microspheres. Following microsphere formation Technosphere particles are freeze dried to form a powder suitable for inhalation. For instance, regular human insulin is incorporated into these microspheres, which is then lyophilised into dry powder for pulmonary administration. Once inhaled, these particles get dissolved in the neutral pH of the lung leading to quick absorption of microencapsulated peptides like insulin or proteins into the systemic circulation. This technosphere technology has been studied for felbamate in mice and parathyroid hormone in humans.

On inhalation, the pH in the lungs will cause dissolution of microspheres, releasing insulin. It rapidly reaches systemic circulation and attains maximum concentration (Cmax) in 15 minutes (Tmax), which is much earlier compared to injectable insulin, and the Cmax is also higher. The mechanism of insulin action remains the same once insulin is absorbed through the lung mucosa.

Technosphere insulin delivered by inhaler has a relative bioavailability of 21–25% compared to sc regular insulin and is also eliminated quickly.3 The T1/2 of inhaled insulin is around 45 minutes.8 This is rapid absorption and elimination resemble endogenous postprandial insulin release. Following inhalation, insulin and FDKP levels in lungs decline over time with values being 12, 1.6, and 0.3% of maximum at 4, 8 and 12 hours postdose, respectively. Clinical work using Technosphere to apply parathyroid hormone, insulin, glucagon and other drugs via pulmonary and subcutaneous administration has already demonstrated the efficacy, reliability and short-term tolerability of this drug delivery system [18-22].

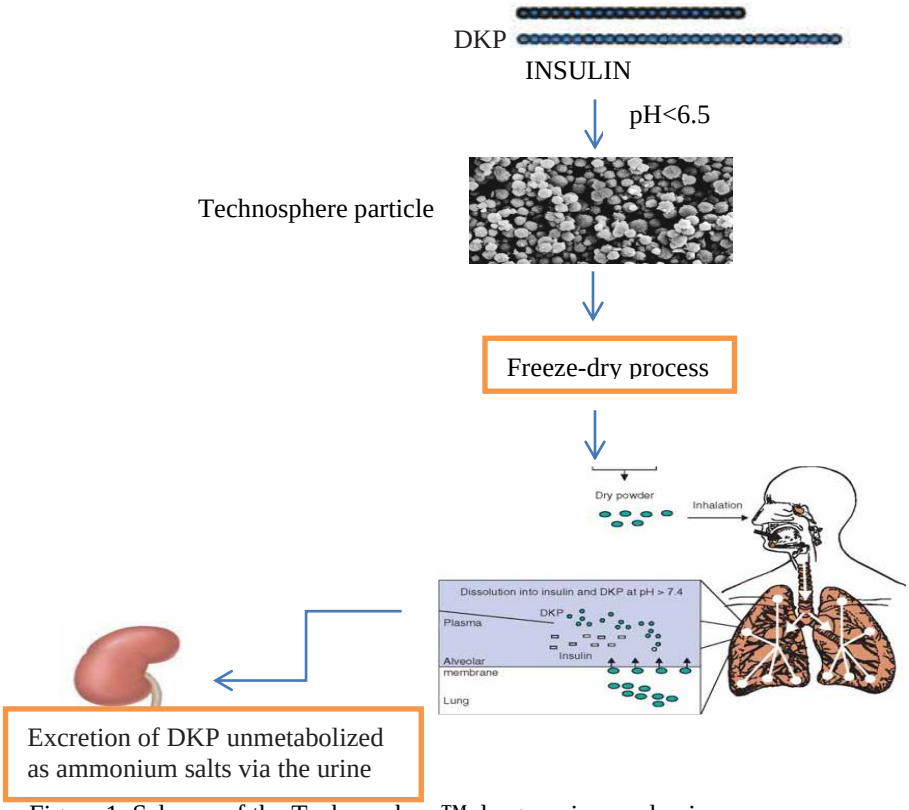

Figure 1. Scheme of the Technosphere™ drug carrier mechanism.
DKP: Diketopiperazine.

III. CLINICAL STUDIES

A. Phase I clinical studies

In the first pilot study with five healthy volunteers, TI was administered by means of a commercially available inhaler (Inhalator M®, Boehringer Ingelheim). Using the euglycaemic clamp technique, the biological efficacy and the pharmacokinetic properties of 100 IU of the new pulmonary formulation was assessed in comparison with 10 IU of subcutaneously injected and 5 IU of intravenously injected regular human insulin (HI). TI was shown to have a very fast onset of systemic uptake (maximum time [Tmax] 13 ± 4 min) in comparison with the subcutaneous injection (121 ± 74 min; $p < 0.001$), resembling the incline of insulin uptake observed with intravenous application (9 ± 4 min). In parallel, the pharmacodynamic profile indicated the peak biological activity after 30 min. This is considerably faster than any reported onset of action of the other actual pulmonary insulin preparations. After inhalation, insulin levels declined to baseline within 3 h. The area under the curve for this time period, however, was more than twice as high as those for intravenous and subcutaneous injections of regular HI in the context of the delivered doses, which requires discussion. The relative bioavailability in the first 3 h was 26 ± 12% (6 h: 16 ± 8%). No adverse events were observed with any of the three single treatment doses and, in particular, no differences were seen in pulmonary function tests performed before and after the study[20]. A Phase I dose–response study evaluated the effect of three different doses (25, 50 and 100 IU) of TI in healthy volunteers, again by means of the euglycaemic clamp technique. The drug was inhaled by 12 healthy volunteers on three different study days, now using a specifically developed inhaler. A step-wise, dose-dependent increase in metabolic activity and systemic insulin uptake was observed. The bioavailability, relative to subcutaneous insulin delivery, over the first 3 h was 46, 42 and 28, respectively. Thesystemic insulin uptake showed a linear dose–response effect
[21, 23]. A pilot study, performed in five healthy volunteers, investigated the distribution pattern of TI particles in the human body. The particles were radiolabelled with 99Tc by means of a passive mass-adhesion labelling technique in a nebuliser chamber, and γ-scintigraphy was applied to assess the distribution of the drug during the inhalation process. The respirable fraction of the radioactively labelled powder was determined to be 52% with an Andersen cascade impactor analysis. It could be shown by γ-camera imaging 4 min after inhalation that the TI particles were equally distributed in the whole lung with detection of 31.7% (range 20.4 – 38.8%) of the emitted dose in the left lung and 27.2% (range 22.7 – 34.4%) in the right. Of the activity, 30% was seen in the oropharynx and 10.7% was detected in the stomach. No activity could be observed in the trachea or the larger bronchi. In the same time, serum insulin levels increased quickly to reach a maximum concentration (Cmax) value of 46 ± 21 μU/ml within 15 min after inhalation. This study demonstrated that the amount of TI that finally reached the alveoli was equally distributed in the whole area of the two lungs. It was concluded that the use of the entire exchange surface of the lung may contribute to the fast absorption of TI into the blood. Although no direct calculation of the bioavailability could be performed in this experiment, it may be noteworthy that the amount of insulin that finally reached the deep lung is comparable with the relative bioavailability of ∼ 30% within the first 6 h after inhalation, which was up to that time seen in the appropriately performed clinical experiments [24].

B. Phase IIa clinical studies

An unpredictable variability of insulin absorption and action has been observed with the subcutaneous injection of regular HI and long-acting basal insulin analogues [25]. Multiple studies have been performed with TI during the past 5 years to investigate intra-subject variability in patients with Type 2 diabetes. The variability of three repeated inhalations of TI 100 IU was assessed by euglycaemic clamp technique in 12 patients with Type 2 diabetes.In this study, the intra-individual variability in Type 2 patients was in the range of the variability observed with regular subcutaneous HI in healthy volunteers. The pharmacokinetic and pharmacodynamic profile that had been reported for TI in the healthy volunteers was confirmed in the Type 2 patients. The mean relative bioavailability within the first 3 h was calculated to be 50% in this study. A second variability study provided a head-to-head comparison of absorption variability for subcutaneous insulin and inhaled TI in patients with Type 2 diabetes. The

individual within-patient variability of the maximal serum insulin concentrations was 14.1 ± 11.3% for 48 IU of pulmonary TI (Cmax 126.7 ± 40.5 μU/ml) compared with 16.9 ± 9.3% for 15 IU of regular HI (Cmax 107.6 ± 57.8 μU/ml, not significant). In comparison with subcutaneous injection of 10 IU of regular HI, pulmonary delivery of TI 48 IU demonstrated a lower variability for maximally achieved serum insulin concentrations and total systemic uptake. Metabolic control as measured by glucose needs was comparable for both treatment regimens [27]. A recent third study, again applying the euglycaemic clamp technique, compared 24 IU of regular subcutaneous HI with inhalation of TI 48 IU in 12 patients with Type 2 diabetes. This study confirms that TI also has a lower variability in biological insulin action as measured by the area under the curve for the glucose infusion rates (e.g., variability of the glucose infusion rate for 180 min: TI 22%; subcutaneous insulin 33%) [28].

C. Phase II clinical studies

The first 3-month randomised, parallel Phase II study was performed in 119 patients with Type 2 diabetes inadequately controlled on diet or oral agents (haemoglobin A1c [HbA1c] 6.6 – 10.0%). They received individual doses of TI or Technosphere placebo prior to each major meal. A significant improvement in HbA1c was seen in both study groups (placebo -0.31%; verum -0.72%). This effect was dependent on the baseline HbA1c and was certainly induced in the placebo arm by the improved care for the patients throughout the study. However, HbA1c was significantly better at end point in the verum arm ($p < 0.005$ between groups at end point). Both Technosphere treatments were well tolerated. No severe hypoglycaemic event occurred in the verum group, and there was no impairment in pulmonary function or induction of antibodies [29]. Although this US Phase II study has already been completed, other Phase II and III studies with TI are currently ongoing worldwide. TI has been shown to effectively lower postprandial blood glucose excursions. The most intriguing treatment option is emerging due to its very fast onset of action, with a rapid increase to already reach Cmax within ~ 15 min. It has been shown that patients with Type 2 diabetes in the early stage of β-cell dysfunction experience an initial lack of the so-called first-phase insulin response. This term describes a short-acting signalling peak of insulin occurring in the plasma shortly before the start of glucose absorption in the intestine tract after food uptake. This peak physiologically mediates the shutdown of hepatic gluconeogenesis, as this production is not required while glucose is absorbed in vast amounts in the gut. The amount of insulin secreted in the first phase equals 3 IU of intravenously injected insulin, and the peak occurs within 10 – 15 min after start of the meal. Depending on the stage of β-cell dysfunction, restoration of this peak may enable the body to regain physiological control over the postprandial glucose excursions [30, 31]. In a pilot study with 12 insulin-treated patients with Type 2 diabetes, the authors have been able to demonstrate that intravenous restoration of first-phase insulin response (with 3 IU) prior to a standardised meal had no effect on postprandial glucose excursions in seven patients, whereas a major improvement was seen in five of the patients. The same clinical efficacy, however, could be achieved by applying TI 12 IU [32]. In a subsequent laboratory investigation, two patient groups were distinct with regard to their β-cell dysfunction status as measured by fasting intact proinsulin concentrations, a recently described highly specific indirect indicator of advanced insulin resistance [33,34]. Using TI to mimic the early-phase response, the relationship between time, insulin concentration and glucose elimination rate (GIR) in a group of 12 subjects with Type 2 diabetes was investigated during a euglycaemic insulin clamp in a second experiment. Each subject received insulin 24 IU s.c. or TI 48 U on separate study days in a crossover design. Glucose disposal rates were reflected by the GIR required maintaining target blood glucose of 120 mg/dl during the 540-min study period. A 48-U dose of TI provided a mean Cmax of 114.8 ± 44.1 mU/l with a median Tmax of +15 min, compared with a Cmax of 63 ± 10.1 mU/l and Tmax of +150 min after insulin 24 IU s.c. TI reached maximal GIR values of 3.33 ± 1.35 mg/kg/min at +45 min, whereas the subcutaneous dose was related to a rate of only 1.58 ± 1.03 mg/kg/min by that time. Moreover, the GIR for the subcutaneous insulin continued to climb to reach its peak of 3.38 ± 1.45 mg/kg/min at +255 min [35]. Both studies support the efficacy of TI in a treatment approach that is somewhat distinct from the current therapy

philosophies, which may have consequences for further understanding and investigation of postprandial glucose control. So far, no studies in patients with Type 1 diabetes have been published. In the ongoing clinical studies, TI can be dosed in 3 IU subcutaneous equivalent steps. It may, therefore, not be the most suitable insulin for Type 1 patients, who require dosing in smaller increments. However, it can be expected that patients with Type 1 diabetes who can adjust to the dosing possibilities will be able to use TI as a replacement for their mealtime insulin injections.

IV. SAFETY ASPECTS

First indications from human [29] and animal [36] experiments point to a low immunogenicity of TI. As mentioned above, initial concerns have been raised by the results with the Exubera dry powder technology, where a threefold increase in insulin antibody titres has been observed within 6 months of treatment as compared with subcutaneous insulin injection [13]. Formation of insulin antibodies is a phenomenon that can be expected in every patient treated with insulin. Antibody titres normally increase within the first 3 – 6 months of treatment to reach a plateau and slowly decrease in the time thereafter. It is of clinical importance to investigate whether antibody titres increase beyond this initial phase, and whether these titres influence the dosing requirements for the insulin [37]. It has been shown for Exubera that the elevated antibodies do not further increase over time and that they also do not impair the efficacy of the applied doses [14-16]. Based on the Technosphere technology, it is to be expected that hydrogen binding and fast absorption may even decrease the antigen exposure from the insulin to the immune system. However, comprehensive long-term evaluations are required to further investigate this phenomenon. The same is true for the assessment of the long-term pulmonary safety and the general tolerability of the Technosphere technology. None of the animal experiments point to a risky situation for the patients in this respect. However, for the technology this is of major importance as technospheres can be applied with comparable success for pulmonary delivery of other pharmaceutically active peptides, such as parathyroid hormone [22, 38, 39]. TI may, therefore, represent the prototype of a whole series of future pulmonary drugs that could benefit from a peak-like pharmacokinetic profile. The question of long-term pulmonary safety can ultimately only be answered by appropriately designed long-term studies, as they will have to be performed by all companies developing pulmonary peptide delivery systems.

V. ADVERSE EFFECTS

Technosphere insulin has been well tolerated by healthy volunteers as well as by people with diabetes. The most common adverse effects were hypo glycaemia and cough.1, 3, 12 Episodes of coughing was more frequent in the first week of treatment and declined by six weeks. Inhaled insulin has the potential to produce amyloid deposits in the lungs.1In the study by Rosenstock et al., a small insignificant, asymptomatic change in pulmonary functions (FEV1, FVC, DLCO [carbon monoxide diffusing lung capacity]) was observed in the Technosphere insulin group and was reversible after three months on cessation. The subjects in the Technosphere insulin group gained less weight than those in the premixed biaspart group at 52 weeks when compared to baseline (+0.9 vs +2.5kg, respectively; p=0.0002).14 Similarly, the occurrence of both mild to moderate hypoglycaemia (47.99 vs 68.88%, $p<0.0001$) and severe hypoglycaemia(4.33 vs 9.97%, $p<0.0066$) was significantly less with Technosphere insulin compared to insulin biaspart.Weight gain was not seen after 12 weeks of Technosphere insulin added to oral antidiabetic drugs.

VI. DRUG INTERACTIONS

There is an increased risk of hypoglycaemia when concurrently used with oral antidiabetic drugs.

VII. DOSE AND DOSAGE FORMS

The Technosphere insulin inhalation powder is available as a cartridge which is inserted into an inhaler and inhaled by mouth one minute before food.19 The cartridges are pre-metred with 15 units or 30 units of insulin (the MedToneTM device was used in clinical trials).20 Recently, MannKind has applied for FDA approval of its second generation inhaler device named DreamboatTM which uses a 10

unit dose of inhaler powder.21 This may cut device cost. Technosphere insulin 15 units is equivalent to 3.8 units of SC rapid-acting insulin analogue.3 The inhalation device is small, compact, and easy to use, store and carry as compared to Exubera insulin. The procedure for loading the insulin powder to administer the Technosphere insulin is simple when compared with previous devices.20 Type 1 diabetes mellitus (T1DM) patients can use insulin glargine or insulin detemir, as basal insulin, once daily in conjunction with bolus Technosphere insulin to reduce prandial insulin requirement.

VIII.CONCLUSION

For more than 75 years, subcutaneous injection has been the primary means for administering insulin. A first pulmonary insulin formulation is currently under review by the regulatory agencies. Amongst the second in line developments, insulin provided to the lung by the Technosphere technology has been shown to possess protruding properties, such as a very rapid onset of action, short duration of action and the highest bioavailability (26 – 50% relative to subcutaneous administration). It may, therefore, help to improve the overall treatment situation of patients with Type 2 diabetes. The development is currently in Phase II/III and the long-term safety and tolerability profile has so far not been established. It is, however, of utmost importance to carefully explore all aspects and implications of delivery of this technology to the lung, as it is a very attractive candidate as a drug carrier mechanism for many peptides and other molecules that currently require parenteral administration by injection or infusion. The development of pulmonary insulin formulations was mainly driven by the potential to overcome the psychological barrier against the use of insulin, especially in patients with Type 2 diabetes fearing the need of injections. Although the competitive developments do not show action profiles that are different to those obtained with subcutaneous injection of short-acting insulin analogues, the pharmacokinetic and pharmacodynamic properties of TI offer several advantages for the Type 2 diabetic patient. The brief interval between administration and appearance of the maximal serum insulin levels, and the rapid onset of action may have a beneficial effect, especially in patients with early Type 2 diabetes lacking the firstphase insulin release. The shorter duration of action of TI, as compared with subcutaneously injected insulin may also better mimic the physiological insulin requirements to cover prandial glucose absorption. The ideal mealtime insulin requires a fast onset within 10 – 15 min and a duration of action of 2 – 3 h. Both requirements are fulfilled by TI. However, long-term safety and tolerability are our remaining concerns. If larger chronic studies are able to confirm the positive safety and tolerability profile that was seen for TI in short-term experiments, this technology will become a very attractive and efficient candidate for prandial insulin delivery.

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