Inhaled human insulin: a clinical perspective

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Delivering insulin via the inhalation route is an exciting concept. Recent progress in inhalation technology has enabled development of inhaled insulin-delivery systems. Exubera® (inhaled human insulin; INH; insulin, human [rDNA origin] Inhalation Powder) is one of several inhaled insulins being developed, and is the first inhaled insulin to obtain regulatory approval in both Europe and the USA for the treatment of diabetes. Initial experience with INH has been encouraging. It has a pharmacokinetic profile that closely mimics physiological insulin response to a meal. As a prandial insulin, its efficacy is comparable to regular subcutaneous insulin. In patients inadequately controlled on oral treatments, regimens using INH alone or in combination with oral agents achieved greater reductions in HbA1c than oral agents alone. INH also appears to be well tolerated and has high patient acceptability. Dislike for injections has often been the reason for patients declining insulin therapy or refusing to intensify existing regimens. Inhaled insulins may appeal to these patients and encourage acceptance of insulin therapy and its intensification more readily and in turn, improve glycemic control.

Insulin therapy has been the mainstay of treatment for patients with Type 1 diabetes and many patients with Type 2 diabetes. Availability of new modified insulins and improved insulin-delivery devices have transformed diabetes management but have not eliminated the need for injections. Dislike of injections, fear of needles and the burden of multiple injections have been among the barriers to insulin initiation [1,2]. Noninvasive insulin may be able to overcome some of these problems. Attempts to develop noninvasive insulin started soon after the discovery of insulin. These were hampered by problems associated with poor bioavailability and unsuitable devices [3]. It is only in the last decade that significant progress in inhalation technology has enabled the development of inhaled insulins. Studies of inhaled insulin appear promising. In clinical trials inhaled human insulin (INH; Exubera®; insulin human [rDNA origin] Inhalation Powder) has so far been shown to be as effective as regular human insulin (RHI) and in patients insufficiently controlled on oral agents, using a regimen of INH alone or in combination with oral agents achieved greater improvements in HbA1c than oral therapies alone. With the worsening burden of diabetes worldwide and the necessity to achieve better diabetes control, there is an increasing need for new therapies. INH may be a valuable addition to the existing choices of therapies and this possibility is reviewed in this article.

Keywords: inhaled human insulin, Type 1 diabetes, Type 2 diabetes

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Unmet needs

The Diabetes Control and Complications trial and the UK Prospective Diabetes Study have firmly established the importance of tight glycemic control in the prevention of long-term complications [4,5]. There is also strong evidence to suggest that early insulin initiation improves glycemic control in most patients with Type 2 diabetes [6]. However, in reality, glycemic control is difficult to achieve and a significant number of patients remain poorly controlled [7]. Many patients (and indeed many health professionals) find the prospect of insulin injections unattractive and often delay insulin initiation or remain on inadequate insulin regimens [8]. This often compromises glycemic control exposing patients to the risk of long-term complications and in turn leading to increased economic burden on healthcare systems. The availability of rapid and long-acting insulins, delivery devices and pumps has extended the choice for both patients and health professionals. Despite this, insulin therapy has remained injection based. Noninvasive insulin administration may encourage patients to accept insulin therapy (including its intensification) more readily and in turn improve glycemic control.

The technology

Several approaches to deliver noninvasive insulin have been attempted but to date, the pulmonary route appears the most promising [9]. The rich vascularity, large absorptive surface and

immunotolerant nature of the lung make it an attractive alternative route for insulin delivery.

Efforts to deliver insulin via the pulmonary route began in the 1920s but were fraught with technical difficulties [10]. Pioneering work by Wigley and colleagues in the 1970s [11] and advances in the understanding of particle dynamics led to the development of improved inhalation devices capable of delivering insulin to the alveoli [12]. Effective delivery of insulin is determined by the particle size. Particles 1–3 µm in diameter reach the alveoli. Particles too small are exhaled and those larger than 5 µm are deposited in the upper airways. Besides particle size, other factors that influence insulin delivery to the periphery of the lung include breath-holding time, inspired volume, inspiratory time and particle velocity. Insulin absorption across the alveolar capillary and epithelial cells occurs by transcytosis. Insulin molecules are then taken up in vesicles by the alveolar epithelial cells, transported by the capillary endothelial cells and, subsequently, released into the bloodstream [13].

Several different insulin-delivery systems are currently in different stages of development. Broadly these use two approaches – dry powdered or liquid insulin formulations. Dry powdered insulin formulations have the ability to deliver larger doses and are more stable at room temperature and less prone to microbial growth. Liquid formulations, on the other hand, are less affected by external humidity and are capable of smaller dose adjustments.

Exubera® has now completed extensive Phase III trials and is the first inhaled insulin formula to obtain regulatory approval in both Europe and the USA. It uses dry-powder insulin packed in blisters of 1 and 3 mg. A single administration of these doses delivers the equivalent of approximately 3 or 8 IU of subcutaneously administered insulin respectively [14]. Two systems (AIR® and AERx®) have begun Phase III clinical trials. The AERx system uses a liquid formulation and an electronically guided system that helps the user to inhale at the required rate and depth. Other systems being developed include Aerodose®, AIR system, Spiros®, Technosphere® and MicroDose dry powder inhaler (DPI) (**Table 1**).

Much of the data presented in this review is from the clinical trials using Exubera INH as it is the most advanced system in development at the time of writing.

Table 1. Inhaled insulin formulations.

Company	Delivery system	Development stage
Dry powdered formulations		
Nektar Therapeutics/Pfizer	Exubera®	Approved in Europe and USA
Mannkind Corporation	Technosphere®	Phase II*
Dura Pharmaceuticals	Spiros®	Phase I*
Microdose Technologies	Microdose DPI®	Phase I*
Liquid formulations		
Aradigm/Novonordisk	AERx iDMS®	Phase III
Alkermes/Eli Lilly	AIR®	Phase III
Aerogen	Aerodose®	Phase II*

**Unconfirmed by manufacturer*

Pharmacological profile

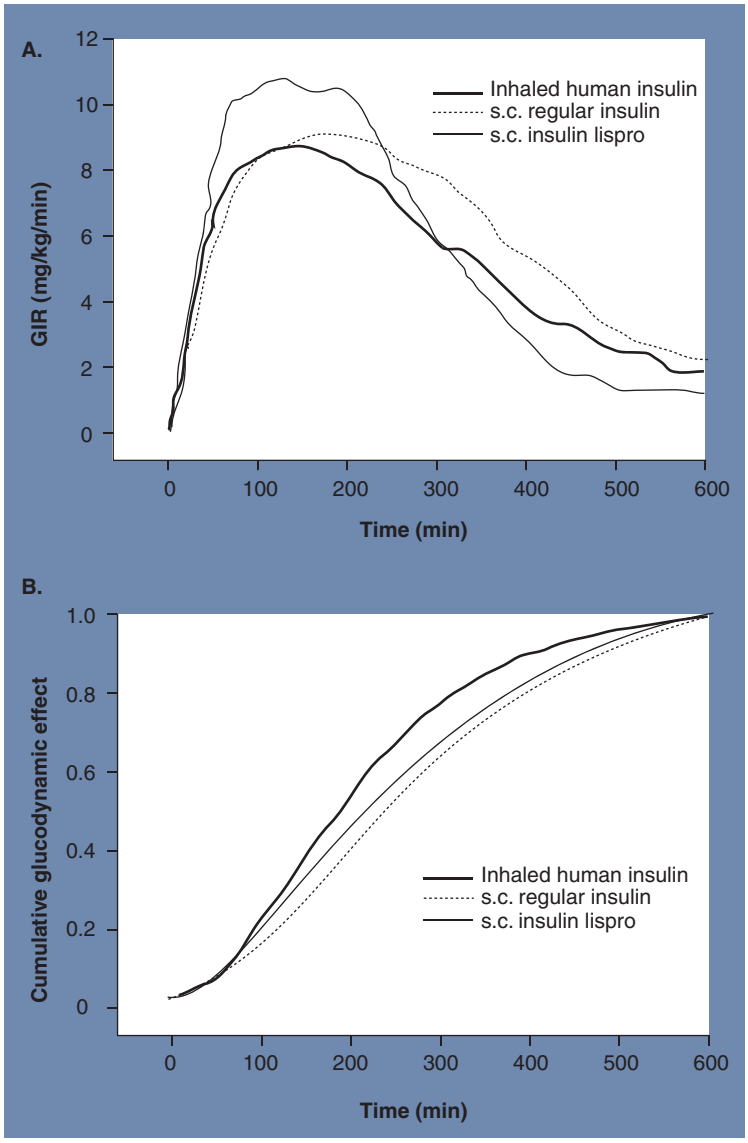
The pharmacokinetic characteristics of inhaled insulins closely mimic physiological insulin response to a meal. Studies in healthy volunteers and patients with Type 1 and Type 2 diabetes have shown that inhaled insulins (Exubera and AERx) can mimic human insulin activity with a faster uptake than regular subcutaneous insulin [15,16]. Depending on the system and the dose administered, time to peak insulin concentrations of 7–80 min have been reported with inhaled insulins compared with 42–274 min with regular subcutaneous insulins [14].

Using the euglycemic glucose clamp technique, the action–time profiles of inhaled, subcutaneous and intravenous insulin were compared in 11 healthy volunteers [17]. Onset of action, and time to maximum metabolic effect and maximum insulin concentrations were all faster (31 vs 54, 108 vs 147 and 24 vs 106 min respectively) with INH compared with subcutaneous insulin.

In a recently published three-way crossover study involving 17 healthy volunteers, INH (Exubera) was compared with subcutaneously administered RHI and insulin lispro (ILP) [16]. In this study, INH had a faster onset of action (32 vs 48 and 41 min, respectively; $p < 0.001$ for INH vs RHI and $p < 0.05$ for INH vs ILP) compared with RHI but comparable to ILP (**Figure 1A**). The duration of action of INH was longer than ILP and comparable to regular subcutaneous insulin (387 vs 313 and 415 min, respectively). The total glucodynamic effect of INH was comparable to both RHI and ILP (**Figure 1B**).

Studies examining intra-patient variability have also confirmed that INH is comparable to RHI [18,19]. In a four-way crossover study, a comparison was made of the pharmacokinetic and pharmacodynamic characteristics of INH versus

Figure 1. Pharmacokinetic profile of inhaled human insulin (Exubera) versus regular subcutaneous and lispro insulin.



A. Baseline-corrected GIRs registered in 17 healthy volunteers after inhalation of 6 mg inhaled human insulin, s.c injection of 18 units regular insulin, and s.c. injection of 18 units insulin lispro (LOESS smoothed data).
B. Cumulative glucodynamic effect. The relative glucose consumption for each of the insulins from the beginning of the glucose clamp to any time point is expressed as a proportion of the total glucose consumption during the entire clamp period (i.e., AUC-$GIR_{0–600}$).
GIR: Glucose infusion rate; s.c.: Subcutaneous.
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subcutaneous insulin in 20 insulin-naïve patients with Type 2 diabetes. At doses required to produce comparable systemic insulin exposure, the intrapatient variability of the pharmacokinetic and pharmacodynamic characteristic of INH were comparable to those of subcutaneous insulin [18].

Bioavailability of INH relative to subcutaneous insulin has been estimated at between 9–22% for different systems. This would suggest that almost ten-times more insulin is needed by the inhalation route than the injected route. However, much of the insulin packaged into the delivery system is actually lost in the upper airways or exhaled. These losses may be as high as 50–80% of that packaged. The actual amount deposited in the lungs is therefore only two- to five-times that of injected insulin [14].

Thus, with a faster onset of action comparable to rapid-acting insulin analogs and a prolonged action similar to RHI, INH appears to have the characteristics desirable of a prandial insulin.

Clinical efficacy

Type 1 diabetes

Several studies have compared the efficacy of INH (Exubera) with regular subcutaneous insulin [20–23]. At the time of this review, no study comparing rapid-acting insulin analogs with INH has been published. Randomized controlled studies comparing INH with regular subcutaneous insulin in patients with Type 1 diabetes have reported similar reductions in HbA1c. This effect appears to be consistent irrespective of the different systems used for insulin delivery [24]. In all the studies, patients receiving INH experienced greater declines in fasting blood glucose compared with patients treated with RHI and data available from the extension studies appear to indicate that this effect is maintained for up to 4 years [25].

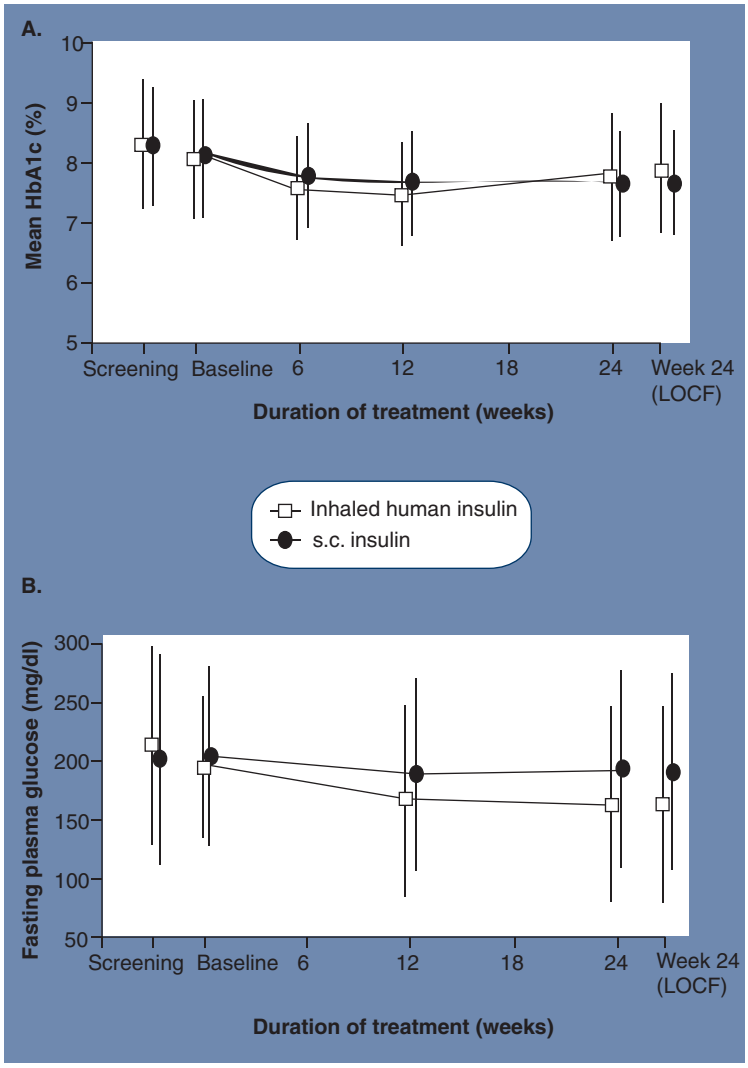
Phase II studies

In a 12-week proof-of-concept study, 72 patients with Type 1 diabetes were randomized to receive either INH plus bedtime Ultralente (n = 35) or RHI plus isophane insulin (NPH) (n = 37). Reduction in HbA1c at the end of 12 weeks was similar in both groups (-0.6 vs -0.8). No significant difference in the incidence or severity of hypoglycemia was observed between the two groups [20].

Phase III studies

Quattrin and colleagues randomized 335 patients with Type 1 diabetes to receive either pre-meal INH with bedtime Ultralente or two to three injections of their usual insulin regimen [21]. Reduction in HbA1c at 24 weeks was comparable in both groups (-0.2 vs -0.4%) (**Figure 2A**). However, patients receiving INH had a greater reduction in fasting and post-prandial glucose and a slightly

Figure 2. Reduction in HbA1c and fasting plasma glucose in patients on inhaled human insulin (Exubera) and regular subcutaneous insulin.



A. HbA1c levels in the inhaled human insulin and subcutaneous insulin groups, respectively, at screening (n = 156/153), baseline (n = 157/155) and weeks 6 (n = 153/147), 12 (n = 154/149) and 24 (n = 153/148). **B.** Mean change in fasting plasma glucose concentration in the inhaled human insulin and subcutaneous insulin groups, respectively, at screening (n = 154/152), baseline (n = 155/154), and weeks 12 (n = 148/149) and 24 (n = 147/144).
LOCF: Last observation carried forward; s.c.: Subcutaneous.
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lower incidence of hypoglycemia (8.6 vs 9 events/subject month; risk ratio [RR]: 0.96 [95% confidence interval [CI]: 0.93–0.99]) (**Figure 2B**).

In another recently published study, INH was compared with regular subcutaneous insulin as part of a basal bolus regimen. A total of 328 patients with Type 1 diabetes received either pre-meal INH or regular insulin along with a basal insulin for 6 months [22]. At the end of the study, reductions in HbA1c were similar in both groups (-0.3 and -0.1%, respectively; adjusted difference -0.16% [95% CI: -0.34–0.01]). Patients in the INH group showed better reductions in fasting glucose and also had fewer hypoglycemic episodes (9.3 vs 9.9; RR: 0.94 [95% CI: 0.91–0.97]).

Type 2 diabetes

Studies in patients with Type 2 diabetes have compared INH with regular subcutaneous insulin as well as with oral agents. In insulin-treated Type 2 diabetes patients the efficacy of INH was comparable to regular insulin. However, in patients on or initiating oral therapy INH was more effective, both when added to existing oral treatments or when compared with another oral agent. In the following discussion of Phase III studies of inhaled insulin in patients with Type 2 diabetes, Exubera (INH) was the product studied.

Subcutaneous insulin-treated

In a 6-month study, 299 patients with Type 2 diabetes on insulin treatment were randomized to receive either pre-meal INH with bedtime Ultralente (n = 149) or at least twice-daily subcutaneous injections of NPH insulin (n = 150) [23]. HbA1c reduction in both groups was similar at the end of 24 weeks (-0.7 and -0.6%, respectively). Patients receiving INH had fewer hypoglycemic episodes (1.4 vs 1.6 events/patient month in INH and RHI groups, respectively) and a greater number of them achieved HbA1c of less than 7% (46.9 vs 31.7%).

INH after diet & exercise

In a study comparing rosiglitazone and INH, 145 patients with Type 2 diabetes received either INH pre-meal or rosiglitazone twice daily [26]. Reductions in HbA1c were observed in the INH and rosiglitazone groups (-2.3 vs -1.4%, adjusted treatment group difference: -0.89% [95% CI: -1.23 to -0.55]). Patients receiving INH or rosiglitazone achieved target HbA1c (HbA1c < 8.0% (83 vs 58%, adjusted odds ratio 7.14 [95% CI: 2.48–20.58], p = 0.0003), HbA1c < 7.0% (44 vs 18%, 4.43 [1.94–10.12]), and HbA1c 6.5% (28 vs 7.5% 5.34 [1.83–15.57]). Hypoglycemia rates were higher with INH than with rosiglitazone (0.7 vs 0.05, episodes/subject-month) (**Figure 3**).

INH in combination with oral agents

In a 3-month study, 68 patients with Type 2 diabetes poorly controlled on oral agents were randomized to either continue their existing therapy

Table 2. Efficacy and safety profile of inhaled human insulin versus subcutaneous insulin in patients with Type 1 and 2 diabetes.

Author	Study design	HbA1c reduction	Hypoglycemic events	Pulmonary function	Refs
Type 1 diabetes					
Skyler *et al.*	12-week, Phase II, randomized, pre-meal INH vs RHI	-0.6 vs -0.8 %	Mild-to-moderate 33 (94.3%) vs 31 (83.8%)	Change from baseline FEV1: -2.17 vs -1.02 DLCO: -5.78 vs -7.71	[20]
Quattrin *et al.*	6-month, randomized, Phase III, pre-meal, INH + bedtime Ultralente vs 2–3 s injections of regular/NPH	-0.2 vs -0.4%	8.6 vs 9.0 events/subject-month	Adjusted difference (INH-subcutaneous) FEV1 :-0.031 (95% CI: -0.082–0.020) DLCO: -1.218 (95% CI: -1.950 to -0.485)	[21]
Skyler *et al.*	6-month, randomized, Phase III, pre-meal INH + twice-daily NPH vs pre-meal RHI + twice-daily NPH	-0.3 vs -0.1%	9.3 vs 9.9 events/subject-month	Adjusted difference (INH-subcutaneous) FEV1: -0.031 (95% CI: -0.082–0.020) DLCO: -1.218 (95% CI: -1.950 to -0.485)	[22]
Type 2 diabetes					
Hollander *et al.*	6-month, randomized, Phase III pre-meal INH + bedtime Ultralente vs 2–3 s injections of regular/NPH	-0.7 vs -0.6%	1.4 vs 1.6 events/subject-month	Adjusted difference (INH-subcutaneous) FEV1: 0.000 (95% CI: -0.048–0.048) DLCO: -0.403 (95% CI: -1.166–0.360)	[23]

CI: Confidence interval; DLCO: Carbon monoxide diffusing capacity (ml/min/mmHg); FEV1: Forced expiratory volume (l) in 1 s; INH: Inhaled human insulin; NPH: Regular human insulin plus isophane insulin; RHI: Regular human insulin.

(n = 36) or to receive additional INH pre-meal (n = 32). At the end of the study, patients treated with INH had greater reductions in HbA1c and fasting glucose. The number of patients achieving the target HbA1c of less than 7% was also higher in the INH group [27].

In a multicenter study conducted in 309 patients with Type 2 diabetes inadequately controlled on oral therapy, a significant reduction in HbA1c was seen in patients who received INH either as monotherapy or as an additional agent to their existing oral therapy (sulfonylurea or repaglinide and metformin or a thiazolidenedione) compared with oral agents alone (HbA1c decline -1.4 vs -1.9 vs -0.2%, respectively). A greater proportion of patients receiving INH achieved HbA1c target of less than 7% and also had marked reductions in post-prandial glucose [28].

In another 24-week study, efficacy of INH was compared with the addition of a further oral agent. Patients poorly controlled on one oral agent (metformin or sulfonylurea) were randomized to receive either pre-meal INH or an additional oral agent (metformin or glibenclamide). Significantly greater declines in HbA1c were observed with INH than either metformin (-2.7% INH vs -2.4% metformin; p = 0.002) or glibenclamide (-2.9% INH vs -2.6% glibenclamide; p = 0.004) [29] (**Table 3**).

Safety profile & tolerability

Hypoglycemia was the most common side effect reported in patients who received INH (Exubera). Overall, hypoglycemic events were comparable (or slightly less) in patients receiving INH to those receiving subcutaneous insulin [20–23]. In patients with Type 2 diabetes, when compared with oral agents, INH-treated patients reported more hypoglycemic events [26–29]. Patients on INH commonly experienced mild-to-moderate cough. However, cough occurred within seconds to minutes of dosing, rarely at night, was rarely productive, declined with time and rarely resulted in discontinuations.

Changes in pulmonary function and increased antibody binding have been some of the potential concerns with INH therapy. However, data from comparator and open-label extension studies using INH poorly show that although there was increased antibody binding in patients who received INH, this was not associated with any

Table 3. Efficacy and safety profile of inhaled human insulin (Exubera) versus oral agents in patients with Type 2 diabetes.

Author	Study design	HbA1c reduction	Achieving HbA1c < 7%	Hypoglycemic events	Pulmonary function	Refs
DeFronzo *et al.*	12-week, randomized, Phase III, INH vs rosiglitazone with diet and exercise	-2.3 vs -1.4	44 vs 18%	0.7 vs 0.05 events/subject-month	Adjusted INH-rosiglitazone difference FEV1: -0.016 (95% CI: -0.079–0.046) DLCO: -0.144 (95% CI: -1.081–0.792)	[26]
Weiss *et al.*	12-week randomized, Phase II INH + OA vs OA	-2.3 vs -0.1	34 vs 0%	0.64 vs 0.06 events/subject-month	Change from baseline % FEV1: -2.7 vs -0.6 DLCO: -3.8 vs -4.7	[27]
Rosenstock *et al.*	12-week, randomized, Phase III INH alone vs INH + OA agents vs OA alone	-1.4 (INH) vs -1.9 (INH + OA) -0.2 (OA)	17 vs 32 vs 1%	1.3 vs 1.7 vs 0.1 events/subject-month	Adjusted treatment difference FEV1: -0.03 (95% CI: -0.09–0.03) DLCO: -0.144 (95% CI: -1.60–0.13) for INH vs OA FEV1: -0.05 (95% CI: -0.11–0.01) DLCO: -0.70 (95% CI: -1.56–0.16) for INH + OA vs OA	[28]
Barnett *et al.*	24-week randomized, Phase III, adjunctive INH or Met or Glib added to previous OA	-2.7 vs -2.4 (INH vs Met) -2.9 vs -2.6 (INH vs Glib)	20.4 vs 14.6% (INH vs Met) 33.9 vs 17.5% (INH vs Glib)	INH–comparator risk ratio 1.11	Adjusted difference (INH–comparator) FEV1: -0.0639 (95% CI: -0.111–0.014) DLCO: -0.144 (95% CI: -1.002–0.452)	[29]

CI: Confidence interval; DLCO: Carbon monoxide diffusing capacity (ml/min/mmHg); FEV1: Forced expiratory volume (l) in 1 s; Glib: Glibenclamide; INH: Inhaled human insulin; Met: Metformin; OA: Oral agent.

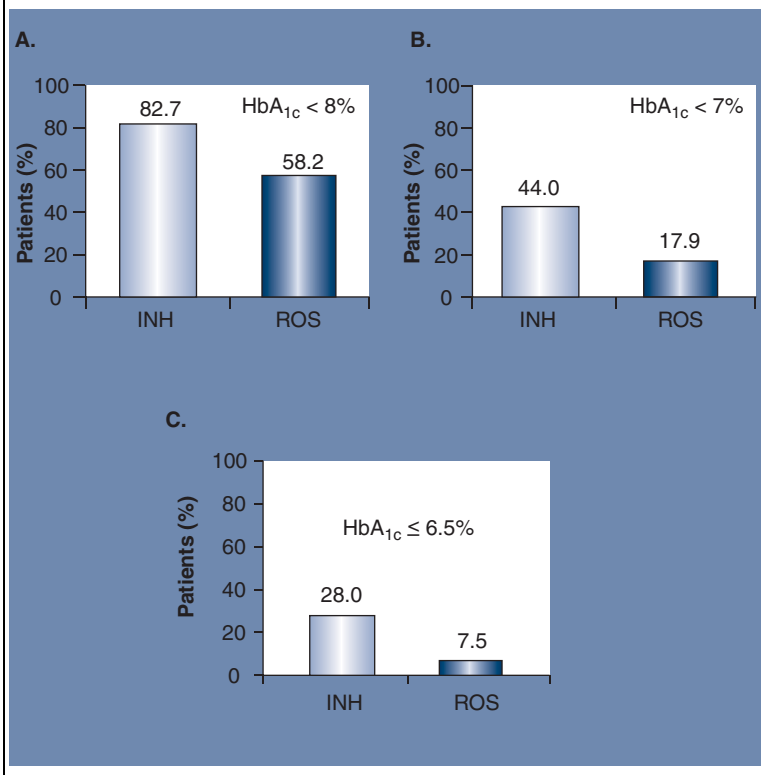
adverse clinical effects [20–23,25,26,28–30]. In a recent analysis of Phase II and III INH trials of Exubera confirmed these findings [31]. In another study involving 47 patients with Type 1 diabetes, increased anti-insulin antibodies were observed in patients receiving INH. However, elevated antibodies were not associated with impaired glycemic control, increased duration of insulin action or hypoglycemic events [32].

Small and clinically insignificant declines in forced expiratory volume in 1 s and carbon monoxide diffusing capacity have also been noted in patients treated with INH (**Tables 2 & 3**). These treatment group differences in changes from baseline pulmonary function are small, occur early, are nonprogressive with up to 2 years of therapy, and reversible upon discontinuation of INH [30]. In comparison with oral agents, INH is associated with more weight gain [26]. Compared with regular subcutaneous insulin, changes in body weight were similar [20,22,23] except in one study, where patients in the INH group gained less weight [21]. While more long-term safety data are awaited, the evidence so far appears to suggest that INH is well tolerated.

Special groups

Clinical trials of INH in patients with Type 1 and 2 diabetes have excluded smokers and asthmatics. Pharmacokinetic studies using AERx inhaled insulin show that absorption is quicker in smokers than in nonsmokers and is slower in asthmatics [33,34]. In a recent study in healthy nondiabetic smokers, absorption of Exubera was compared at baseline, after smoking cessation and smoking resumption. Although smoking cessation had some beneficial effect, this was reversed following smoking resumption [35]. In this context, it is worth mentioning that smokers must be actively encouraged to quit, regardless of whether or not they anticipate using INH. Exubera is

Figure 3. Percentage of patients achieving target glycemic levels in the inhaled human insulin (Exubera) and rosiglitazone groups.



Percentage of patients achieving target glycemic levels in the INH and ROS groups. Adjusted OR INH-ROS **(A)** 7.14 [95% CI: 2.48–20.58]; p = 0.0003; **(B)** 4.43 [95% CI: 1.94–10.12]and **(C)** 5.34 [95% CI: 1.83–15.57].
CI: Confidence interval; INH: Inhaled human insulin Exubera; OR: Odds ratio; ROS: Rosiglitazone.

contraindicated in patients who smoked or who have smoked in the previous 6 months prior to initiating therapy. Intercurrent illness, especially involving the respiratory system, can affect the availability of insulin. In a recent study, it was reported that there were no statistically significant differences in pharmacodynamics or pharmacokinetics of AERx during an upper respiratory infection [36]. However, more studies are needed to clarify this issue. Effects of exercise, pregnancy, alcohol and concomitant medications on the pharmacology of INH have also not been studied in detail and future studies need to address these issues.

Patient satisfaction & acceptability

Several studies examining patient satisfaction have reported greater acceptance and satisfaction in patients treated with INH [21,23,37–42]. In a pooled analysis of two 12-week parent studies and a 1-year extension study in patients with Type 1 and 2 diabetes, INH was preferred over subcutaneous insulin [38]. Many patients receiving subcutaneous insulin switched to INH and a greater proportion of those on INH chose to continue with it. Overall, satisfaction scores were significantly better for INH in terms of treatment satisfaction (37.9 vs 3.1%, $p < 0.01$) and ease of use (43.2 vs -0.9%: $p < 0.01$). In another study involving patients with Type 2 diabetes poorly controlled on oral therapy, availability of INH increased the number of patients who would accept insulin therapy. Patients were three-times more likely to accept insulin when the INH option was available [39]. Treatment satisfaction with INH was shown to be comparable to oral agents in both the adjunctive INH versus metformin and adjunctive INH plus sulfonylurea (glibenclamide) studies in patients with Type 2 diabetes [29]. In the study evaluating INH monotherapy and adjunctive INH plus oral agents versus their existing oral agent therapy [28], overall satisfaction remained unchanged for oral agents, whereas it improved significantly for both INH treatment groups [44].

Cost-effectiveness

Cost of treatment with INH is expected to be high. The increased cost is largely related to the cost of innovation and to a lesser extent, larger doses of insulin used. As yet, no data are available to assess the costs and benefits of treatment with INH. However, it is likely that improved patient satisfaction and treatment adherence may lead to better glycemic control and improved long-term outcomes, potentially reducing the burden of overall costs for diabetes and its complications.

Expert commentary

INH is a potentially important breakthrough in the field of diabetes and has generated many expectations. However, new therapies need to be evaluated against those currently in use before being accepted as standard treatment. Data available from the clinical studies up to now suggest that INH is effective and well tolerated. In studies comparing INH with RHI, INH has been shown to be at least as effective as subcutaneously injected regular insulin. This is true irrespective of the Type of diabetes and, importantly, efficacy appears to be maintained long-term. In addition, more patients treated with INH had better fasting glucose profiles and achieved HbA1c targets. INH also has a favorable pharmacokinetic profile suitable for pre-meal administration. However, most of the studies have

Highlights

- Of the several approaches to noninvasive insulin delivery, the pulmonary route appears to be the most promising. Several different systems of inhaled insulin are currently being developed. Exubera® is the most advanced of these and was recently approved in the USA and EU for the treatment of adults with diabetes.
- The pharmacokinetic profile of inhaled human insulin (INH, Exubera) closely mimics the physiological response to a meal. It has an onset of action comparable to rapid-acting analogs and a duration similar to regular subcutaneous insulin.
- When given pre-meal in combination with a long-acting insulin, the efficacy of INH is comparable to regular subcutaneous insulin and in patients insufficiently controlled on oral agents, using a regimen of Exubera alone or in combination with oral agents achieved greater improvements in HbA1c compared with oral agents alone.
- INH is well tolerated, with a similar incidence and severity of hypoglycemia to subcutaneous insulin. Changes in lung function have been shown to be small, nonprogressive and reversible, while insulin antibodies are not associated with adverse clinical outcomes, both in the short-term and longer term extension studies of Exubera.
- Availability of INH may make insulin treatment more acceptable and it is hoped that will help patients adhere to their treatments leading to better clinical outcomes.

compared INH with RHI and studies comparing rapid-acting insulin analogs are awaited. However, given its pharmacokinetic profile it is likely that INH will show similar efficacy to rapid-acting analogs.

Safety data from clinical trials indicate that INH is well tolerated. Hypoglycemic events reported with INH are at least comparable (if not less frequent) to those with RHI. Most short-term studies have observed elevated antibody levels and changes in lung function. These latter changes have been reported to be nonprogressive in long-term extension studies of INH. Neither the raised antibody levels nor changes in lung function were clinically significant. While this is reassuring, more safety data will be needed to convince patients and healthcare professionals regarding its long-term safety. Studies are planned and pulmonary function monitoring is recommended prior to initiating INH therapy and at regular intervals thereafter.

For the majority of patients well controlled on their current regimens, a change in therapy may not be necessary. However, in those patients who are not attaining optimal glucose control with currently available insulin therapies, INH may be an attractive option. This includes patients with Type 1 and 2 diabetes who require multiple injections as well as patients with Type 2 diabetes who are poorly controlled on oral therapy. Current evidence suggests that INH is well accepted by patients and this may encourage them to start or intensify insulin treatment more readily. Although a direct relationship between improved patient satisfaction and glycemic control has not been established with INH, it is not unreasonable to consider that any therapy that encourages adherence would improve clinical outcomes.

Despite these positive attributes, INH has a number of limitations. Much of the available evidence does not include smokers, asthmatics and those with other respiratory disorders. Similarly, effects of INH in the elderly are also not known. Several other factors such as exercise, intercurrent illness, concomitant medication and alcohol are known to alter insulin requirements. The influence of these factors also needs to be understood. More information on these aspects with INH use will be clarified as experience with these products is extended to a large number of patients. INH is also likely to be expensive and therefore the cost of treatment must be carefully balanced against the benefits.

Outlook

Availability of INH may make insulin treatment more acceptable. Exubera is indicated in adults with Type 2 diabetes not adequately controlled with oral agents and requiring insulin therapy, and in adults with Type 1 diabetes in addition to long- or intermediate-acting subcutaneous insulin for whom the potential benefits of adding INH outweigh potential safety concerns. However, its use might be extended to other patient populations. From a purely clinical point of view, it is hoped that this approach may encourage more patients to initiate, intensify and adhere to their insulin-based treatments. This should in turn lead to better clinical outcomes

Only the short-acting formulations of inhaled insulin are in clinical development at present. Most patients needing insulin will still have to take at least one injection of basal or long-acting insulin. It is therefore unlikely that the need for injections will be eliminated entirely. Success of short-acting inhaled insulins may, however, inspire research in the development of long-acting preparations. Similarly, it can be hoped that further advances in technology will lead to the development of newer devices that increase the bioavailability and make INH more desirable.

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