

# Optimizing Glycemic Control: The Search for Feasible Noninvasive Insulin Delivery Systems

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*This paper was presented in part at the Canadian Diabetes Association/Canadian Society of Endocrinology and Metabolism Professional Conference, October 17–20, 2001, Edmonton, Alberta, Canada*

## A B S T R A C T

Despite the well-known benefit of glycemic control in preventing the complications of diabetes, and insulin's role in glycemic control, intensive insulin therapy (IIT) has not gained widespread clinical acceptance due to psychological, physiological and anatomical barriers. To overcome many of these barriers, noninvasive routes of insulin delivery have been evaluated. Although many are still in the early stages of development, results have been promising. Currently, the most feasible approaches are pulmonary delivery (inhaled insulin), which has progressed through phase III trials, and buccal spray. A major advantage of inhaled insulin is its pharmacokinetic (PK) profile, which appears to be comparable to that of the newer insulin analogues and may allow for a more physiological insulin secretion profile. The convenience of the alternative approaches, and related improved patient satisfaction, may lead to better patient compliance and, consequently, improved glycemic control.

## R É S U M É

Même si on connaît bien les avantages de l'équilibre glycémique au chapitre de la prévention des complications du diabète et le rôle de l'insuline dans l'équilibre glycémique, l'insulinothérapie intensive ne s'est pas généralisée en clinique en raison d'obstacles de nature psychologique, physiologique et anatomique. Pour surmonter plusieurs de ces obstacles, on a évalué des voies non effractives d'administration d'insuline. Plusieurs en sont encore aux stades initiaux de développement, mais les résultats sont prometteurs. Actuellement, les méthodes les plus pratiques sont l'administration pulmonaire (inhalation d'insuline), qui en est aux essais de phase III, et la vaporisation buccale. Un des principaux avantages de l'administration d'insuline par inhalation est au niveau de la pharmacocinétique : elle semble comparable à celle des analogues de l'insuline les plus récents et pourrait ressembler davantage à la sécrétion d'insuline physiologique. La commodité de ces nouvelles méthodes et l'amélioration de la satisfaction des patients qui en résulte pourraient améliorer la fidélité au traitement et, partant, l'équilibre glycémique.

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## INTRODUCTION

Since its discovery, insulin has been the mainstay of treatment for patients with type 1 diabetes. For patients with type 2 diabetes, clinicians have traditionally relied on oral antihyperglycemic agents, as their mechanisms of action are designed to overcome the pathophysiological abnormalities recognized to be present (1,2). However, with observations acquired from long-term, prospective trials, it is now recognized that patients with type 2 diabetes undergo various stages of clinical management as beta cell dysfunction progresses and insulin secretory capacity declines, necessitating the use of multiple oral therapies to achieve glycemic control (3,4). Thus, therapeutic combinations of different classes of oral agents have been shown to have additional glycemic benefit, and combination oral therapy is now routine (3,4).

Due to continued progression of the disease, however, even combination oral antihyperglycemic therapy may prove inadequate to control hyperglycemia, as determined by failure to achieve target HbA<sub>1c</sub> levels. In this regard, for patients with type 2 diabetes, exogenous insulin therapy may be appropriate to achieve glycemic control, either as monotherapy or in combination with oral agents (4,5). As such, the use of insulin earlier in the management of type 2 diabetes has received considerable attention (6). Although an estimated 40% of patients with type 2 diabetes in the United States (US) currently receive exogenous insulin therapy, this use of insulin appears to be more widely accepted in Europe than in the US (7,8). For example, the European Diabetes Policy Group has suggested guidelines for diabetes care that recommend using insulin in patients with type 2 diabetes who have HbA<sub>1c</sub> levels >7.5% (7). In attempts to achieve good glycemic control, exogenous insulin therapy can be considered the gold standard, as the dose can be titrated to achieve the desired glycemic target.

Thus, insulin has emerged as a more viable treatment option much earlier in the disease process in patients with type 2 diabetes. In addition, it is well documented that, in patients with type 1 diabetes, multiple daily injection therapy (i.e. intensive insulin therapy [IIT]) achieves tight glycemic control and reduces complications associated with diabetes (9). Nevertheless, despite the demonstrated benefits of IIT, this approach has not gained widespread acceptance in clinical practice (10) due to barriers regarding the initiation of insulin therapy (for patients with type 2 diabetes) and in advancing to IIT (for patients with type 1 and type 2 diabetes).

## BARRIERS TO IIT

### Patient compliance

IIT requires a substantial commitment from the patient, who must administer multiple daily injections, check blood glucose (BG) levels frequently and carry insulin and supplies at work and play. The inconvenience of these factors alone may discourage patients from advancing to more intensive insulin therapy. Patients with type 2 diabetes may also perceive that advancing to insulin therapy is related to a serious progression

of their disease state or may feel anxiety about injections. In a recent survey of insulin-treated patients with either type 1 or type 2 diabetes, 14% of respondents avoided injections because of anxiety and 42% refused to increase their number of injections. Of the 28% who considered themselves “highly anxious,” approximately 45% avoided injections and were extremely troubled by the idea of giving themselves multiple injections (11).

### Weight gain/hypoglycemia

Both clinicians and patients may be concerned about the potential side effects of weight gain and hypoglycemia with insulin therapy (12). Clinical observations suggest that weight gain may be associated with the large doses of insulin required to achieve a reduction in hyperglycemia and overcome insulin resistance in patients with type 2 diabetes. Furthermore, the pharmacokinetic (PK) profile of regular subcutaneous (SC) insulin is not ideal for physiological insulin replacement, as it is absorbed slowly and has a delayed onset of action, thus predisposing the patient to hypoglycemia. However, newer insulin formulations and dosing regimens provide a more physiological approach to insulin therapy and have helped to ameliorate these side effects.

### Cardiovascular risk

The issue of whether exogenous insulin therapy increases cardiovascular (CV) risk in patients with type 2 diabetes is much debated. Results from the United Kingdom Prospective Diabetes Study (UKPDS) suggest that exogenous insulin treatment does not worsen cardiovascular disease (CVD) and probably has favourable effects (13). These findings are supported by an observed 16% reduction in the risk of combined fatal and nonfatal myocardial infarction (MI) and sudden death in those who received intensive therapy in the UKPDS, a figure that approached statistical significance (13). Additional evidence supporting the favourable effects of insulin therapy on the CV system was provided by the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, which demonstrated that IIT in the setting of acute CV events improved long-term survival in patients with diabetes (14).

### Healthcare practitioner limitations

A time commitment is required by healthcare practitioners to successfully implement IIT (15). In addition, the practitioner must have access to resources to educate patients about insulin formulations, home BG monitoring, carbohydrate counting and treatment of hypoglycemia. Therefore, lack of ready access to diabetes educators and nutritionists may limit patients' successful implementation of insulin therapy.

### Insulin formulation limitations

The PK and pharmacodynamic (PD) shortcomings of previous insulin preparations have also limited widespread acceptance

of IIT. The time-action profile of regular SC insulin (i.e. slower onset and more prolonged duration of action) does not mirror normal physiology by failing to provide early insulin release in response to a meal (16,17). The patient with type 2 diabetes lacks the first phase of insulin release and will require replacement of the meal-related bolus in insulin secretion in addition to basal control (18). As a result, insulin doses large enough to lower postprandial increases in BG levels often predispose patients to later episodes of hypoglycemia, as well as hyperinsulinemia and weight gain. Lower doses, which decrease the risk of hypoglycemia, fail to provide adequate control of postprandial blood glucose (PPG) levels, leading to inadequate HbA<sub>1c</sub> control (15). In addition, optimal timing of injections 30 to 60 minutes before meals may require inconvenient delays. The new long-acting formulations (insulin glargine [Lantus<sup>®</sup>]), in addition to the new rapid-acting insulin analogues (lispro [Humalog<sup>®</sup>] and aspart [NovoRapid<sup>®</sup>]), have addressed these concerns. Lispro and aspart have a more rapid onset and shorter duration of action than regular insulin (19,20). Thus, regimens that combine prandial rapid-acting lispro or aspart with a longer-acting insulin (e.g. glargine) for basal insulin better mimic a normal and more physiological insulin profile.

It is apparent that practical and psychological hurdles contribute to resistance to insulin therapy in patients with type 2 diabetes and to IIT in patients with type 1 and 2 diabetes. The inertia in advancing to more aggressive therapy may adversely influence compliance and greatly interfere with the clinical goal of achieving BG control.

## NONINVASIVE INSULIN DELIVERY SYSTEMS

The major goals when considering a practical, noninvasive insulin delivery system are to overcome the primary limitation associated with conventional insulin regimens by eliminating injections and to preserve a more physiological insulin profile. Innovations have made self-injection easier; for example, the insulin pen injector is small, convenient, disposable and allows the desired dose of insulin to be selected with precision (21). It uses smaller-gauge needles that may result in less painful injections than conventional needles (22). Elucidation of insulin's structure has allowed for development of newer analogues that provide a more physiological insulin

PK profile (19,20,23). Achieving the above-stated goals for noninvasive insulin delivery (i.e. eliminating injections and providing a more physiological insulin secretory profile) will allow for more intensive insulin delivery with a regimen clinically proven to significantly improve BG levels and reduce complications, while enhancing patient compliance. Such goals are lofty, but several research approaches are undergoing evaluation to achieve them (Table 1).

### Jet injectors

Jet injectors administer insulin without needles by delivering a high-pressure stream of insulin into SC tissues. These devices, first developed 40 years ago, have limited use in the treatment of diabetes (21,24). The advantage initially suggested for jet injectors was that the insulin dose delivered was more precise and more quickly absorbed than with SC needle delivery; however, it appears that the duration of intermediate-acting insulin may be decreased with the use of these devices, which can defeat glycemic control (24). Moreover, although the absence of needles is appealing, the discomfort associated with jet injectors is reported to be comparable to that associated with injections (21). These devices, however, can potentially benefit a patient who has severe anxiety regarding needles.

### Iontophoresis

Transdermal delivery of insulin by direct electrical current, a process referred to as iontophoresis, has been tested in laboratory animals. Iontophoresis is similar to the transdermal patches currently used to deliver nicotine for smoking cessation programs or hormone replacement therapy (HRT) for postmenopausal women. However, iontophoresis uses low-level electrical current to accelerate delivery of drug ions into the skin and surrounding tissues. In a study of rats with diabetes, iontophoretic delivery of bovine insulin produced a concentration-dependent reduction in BG levels (25). The method did not appear to be as effective in rats that had not been depilated, suggesting that either the depilation was effective in reducing the skin's barrier function or the creams used with the iontophoretic device acted as a penetration enhancer only in animals that had been treated in advance with a depilatory cream instead of having their hair removed with scissors. In contrast, iontophoretic delivery of a

**Table 1. Research approaches to noninvasive insulin delivery**

<b>Device</b>	<b>Method of delivery</b>
Jet injectors	Devices that administer insulin by delivering a high-pressure stream of insulin into tissues
Iontophoresis	Transdermal delivery of insulin by a direct electrical current
Ultrasound	Process by which sound waves increase, by several fold, the permeability of human skin to macromolecules
Transfersomes	Composites of pharmaceutically accepted ingredients flexible enough to pass through pores in the skin; transfersomes are much smaller than their components
Intranasal	Use of nasal membranes as absorptive surface for insulin
Oral	Uptake of insulin occurring within the gastrointestinal tract or buccal mucosa
Pulmonary	Insulin uptake occurring in the highly vascularized alveoli of the lung

monomeric human insulin analogue produced a significant reduction in BG in rats through intact (untreated) skin (25). Factors affecting transdermal absorption and delivery of insulin with this technique require further study before it becomes a clinical reality.

### Low-frequency ultrasound

The use of low-frequency ultrasound has been demonstrated to increase, by several fold, the permeability of human skin to macromolecules, and this technique has been evaluated as a means of noninvasively administering insulin. It has been suggested that the permeability achieved with ultrasound techniques given for 1 hour approximately 3 times per day can allow a typical daily dose of insulin to be delivered (26). Although this approach is potentially feasible, it provides a rate of insulin delivery that may be too slow to be a viable clinical option for preprandial use. Whether this approach will be appropriate to meet basal insulin needs requires further elucidation.

### Transfersomes

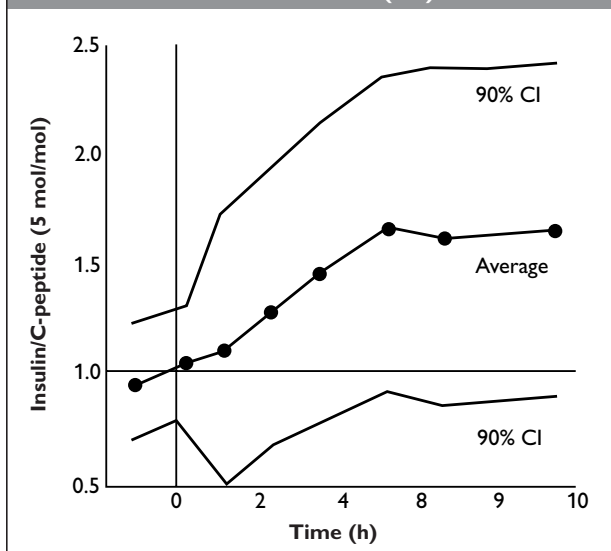
Transfersomes (composite phosphatidylcholine-based vesicles) are composites of pharmaceutical ingredients flexible enough to pass through pores in the skin much smaller than the pharmaceutical ingredients themselves. Transfersomes have the property of deformability, which facilitates their rapid penetration through the intercellular lipids of the skin; indeed, transfersomes pass through pores with an efficacy similar to water, despite being approximately 1000 times larger. This technology therefore has the potential to deliver

macromolecules, such as insulin, across the skin barrier and has demonstrated efficacy in transdermally delivering local and systemic steroids, proteins and other hydrophilic macromolecules. Early tests performed in mice and humans showed that when the vesicles are loaded with insulin and applied to intact skin in sufficient quantity, insulin may be transported with at least 50% of the bioefficiency of an SC injection (Figure 1) (27). It is conceivable that this approach may provide basal insulin coverage; with the present technology, it is estimated that a skin surface area of approximately 40 cm<sup>2</sup> is sufficient to provide the daily basal insulin requirement of most patients with type 1 diabetes (27). Additional studies are required to determine the clinical utility of this approach.

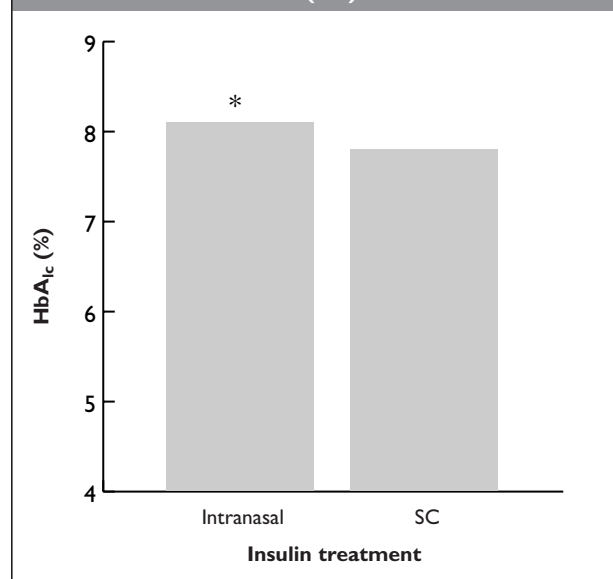
### Intranasal delivery

Intranasal insulin delivery was first suggested 65 years ago, but it was not until the 1980s that this approach was investigated seriously (21,28). The major problem associated with intranasal insulin delivery is poor bioavailability across the mucous membranes. In 1995, Hilsted and colleagues evaluated the efficacy of intranasal insulin in 31 patients with type 1 diabetes (29). Subjects were treated with prandial intranasal insulin for 1 month and with prandial SC regular insulin for another month in an open, crossover, randomized trial (29). The required doses of intranasal insulin were approximately 20 times higher than those needed with SC injection; no difference in the number of hypoglycemic episodes was observed between SC and intranasal delivery. Despite the large doses of insulin, markers of metabolic control worsened

**Figure 1. Average change in systemic insulin/C-peptide molar ratio as a function of time after epicutaneous Transfersulin administrations (6 experiments) in an individual without diabetes (27)**



**Figure 2. HbA<sub>1c</sub> concentrations after intranasal vs. SC insulin treatment (29)**

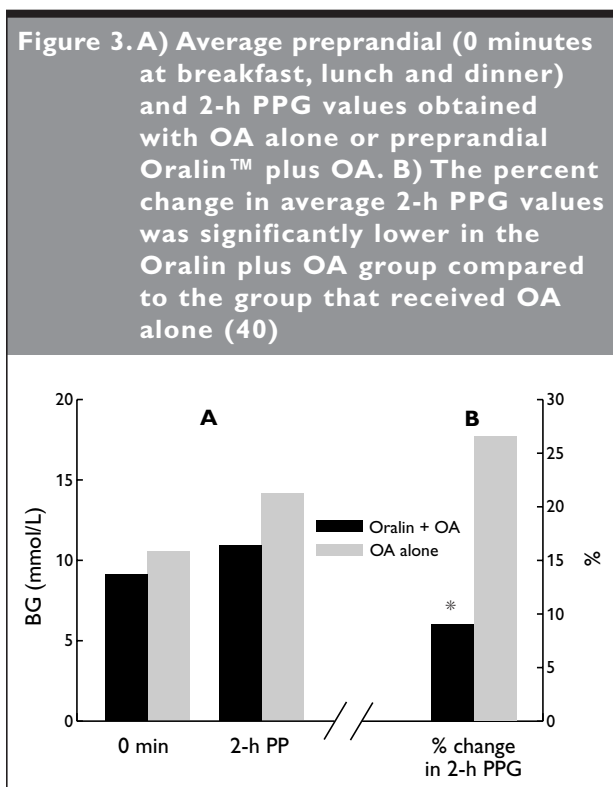


\*p<0.01

SC = subcutaneous

slightly, but significantly, during intranasal insulin treatment (Figure 2) (29).

A number of absorption-enhancing compounds, e.g. bile salts and polyethylene ether derivatives, have been evaluated as vehicles to enhance the bioavailability of intranasal insulin. This resulted in more rapid absorption and effective biological activity of intranasal insulin, but may increase the risk of nasal irritation (30,31). In a crossover comparison of preprandial intranasal insulin (60 or 120 units) and placebo in 17 subjects with type 2 diabetes, incremental PPG was reduced with intranasal insulin at both 60 and 120 minutes (30). More recent studies have also shown the feasibility of this approach. Specifically, the local tolerance and metabolic efficacy of a lyophilized nasal insulin preparation was evaluated in 10 severely hyperglycemic patients with type 2 diabetes. The study included 2 4-month randomized periods of preprandial intranasal insulin doses combined with evening NPH, if desired control was not achieved, or 2 NPH injections daily. Use of intranasal insulin (with or without NPH) was associated with glycemic control similar to that achieved with the use of twice-daily NPH (32). Intranasal insulin has shown promise, but further studies are required to establish long-term safety and efficacy before it is accepted as a viable route of noninvasive insulin delivery.



\* $p < 0.001$

BG = blood glucose

OA = oral antihyperglycemic agents

PP = postprandial

PPG = postprandial blood glucose

### Oral insulin

On practical grounds, oral insulin administration, where uptake occurs either in the gastrointestinal tract or the buccal mucosa, is a very desirable approach as it offers specific advantages of convenience and thus has the potential to greatly improve patient compliance. A theoretical advantage of absorption of oral insulin via the gastrointestinal tract is that it would more closely mirror the enterohepatic transport of endogenous insulin (33). Unfortunately, administration of insulin via the gastrointestinal tract has numerous barriers to overcome before it becomes a clinical reality. Of primary concern is limited bioavailability (i.e.  $\leq 0.5\%$ ), as insulin molecules tend to be too large and hydrophilic to cross the mucosa; second, insulin molecules may undergo extensive enzymatic and chemical degradation within the enzymatic barrier of the gastrointestinal tract mucosa (34). In an effort to overcome these anatomical and physiological barriers, the use of protease inhibitors (to limit degradation) and absorption enhancers has been evaluated (33,35). The process of enclosing insulin within microspheres, thereby protecting it against hydrolyzation or enzymatic degradation, has also been proposed (36). Studies have been reported for hexyl-insulin-monoconjugate-2 (HIM2), a native recombinant insulin with a small polyethylene glycol (PEG) 7-hexyl group attached to the position B29 amino acid lysine. Clinical trials suggest that oral HIM2 has a bioavailability of approximately 5% and may have an acceptable BG-lowering effect (37). Although such an approach with conjugated insulin holds promise for the future, substantially more clinical research is required. Furthermore, the feasibility of using an oral delivery agent to facilitate human insulin absorption following oral administration has been more recently reported (38). Thus, strategies to overcome the barriers to oral insulin delivery continue to be developed.

### Buccal delivery

Oral insulin delivery that relies on absorption of insulin in the buccal mucosa (i.e. buccal delivery) has advanced to a phase of testing that suggests that this approach may be clinically feasible. Insulin delivered by the buccal route is reported to be rapidly absorbed into the systemic circulation through the buccal mucosa and the oropharynx (39). Several systems for buccal delivery have been clinically evaluated, including Oralin™, a liquid aerosol preparation developed in Canada (40,41). In subjects with type 2 diabetes, preprandial administration of buccal insulin was found to be comparable to SC insulin in terms of PPG, insulin and C-peptide levels (41). In a study of 24 subjects with type 2 diabetes who had not achieved glycemic control with oral antihyperglycemic therapy, the addition of approximately 100 units of buccal insulin before each meal to oral antihyperglycemic therapy significantly decreased PPG levels compared to the use of oral agents alone (10.3 vs. 14.5 mmol/L) (Figure 3) (40). Furthermore, an oral insulin formulation consisting of

insulin delivered by an aerosol spray with a RapidMist™ device has recently been reported to have a PK profile similar to that of insulin lispro (42). Specifically, a study of 22 patients with well-controlled type 1 diabetes compared the PK profiles of regular insulin, lispro and oral insulin spray (with an absorption enhancer). However, since only 4 patients received insulin lispro, the sample size was too small to determine significant differences between treatment groups (42). Another study of buccal insulin in 30 patients with type 1 diabetes found no significant differences in PPG control between those treated with buccal insulin and those treated with SC insulin, although plasma insulin levels were reported to peak more rapidly with buccal administration (43). Although the preliminary efficacy studies may appear promising, safety reports of buccal insulin are scarce and the majority of the aforementioned studies did not assess side effects.

### Pulmonary delivery

The physiological and anatomical barriers that limit the successful implementation of other routes of noninvasive insulin delivery do not appear to be of major concern in consideration of the feasibility of pulmonary delivery of insulin, due in large part to the favourable anatomy of the lung. Specifically, the lung is characterized by hundreds of millions of highly vascularized alveoli, where drug absorption takes place, and has an extensive surface area (estimated to be approximately 60 to 80 m<sup>2</sup>) that provides for rapid drug absorption. Absorption of insulin is further aided by the fact that the alveolar walls are extremely thin with intercellular gaps that make the alveoli, compared to other mucosal beds, more permeable to large proteins. Thus, even without absorption enhancers, insulin uptake across the pulmonary mucosa is far greater than that observed across either nasal or buccal surfaces (39).

The concept of pulmonary delivery of insulin dates from 1925, just a few years after Banting and Best reported their

discovery of insulin (44). The modern era, however, began approximately 30 years ago. In 1971, Wigley and colleagues demonstrated that insulin aerolized via a nebulizer had a hypoglycemic effect in rabbits (45). Furthermore, increased levels of plasma immunoreactive insulin were demonstrated in 4 subjects with diabetes and 3 subjects without diabetes (45). Since that time, significant progress has been made to define and characterize the PD profile of insulin delivered via the lung.

Heinemann and colleagues, in a study of 11 healthy subjects, used the euglycemic clamp technique to compare the PD profiles of 99 units of microcrystalline dry human insulin powder, 10 units of SC regular human insulin, and 5 units of intravenous (IV) regular human insulin (46). The onset of action of inhaled insulin (31 vs. 52 minutes) and maximal metabolic response (108 vs. 147 minutes) were more rapid than those of SC insulin. The bioavailability of inhaled insulin was approximately 10% compared to injected insulin (46). Heise and colleagues compared the time-action profile of inhaled insulin (6 mg) to that of SC regular insulin (18 units) and insulin lispro (18 units) using the euglycemic glucose clamp technique in 18 healthy, nonsmoking male subjects (47). The inhaled insulin demonstrated a faster onset of action than SC regular insulin and lispro of 32, 48 and 40 minutes, respectively, whereas its duration of action was between that of regular insulin and lispro (382, 413 and 309 minutes, respectively). The time-concentration profile of pulmonary insulin delivery therefore has been shown to be more physiological than that of conventional regular insulin in that it mimics normal insulin secretion.

Similar data for the PK profile of inhaled insulin have also been shown in subjects with diabetes. In a study of 7 subjects with type 2 diabetes, insulin levels peaked 43 minutes after administration of inhaled insulin vs. 64 minutes with SC regular insulin. The bioavailability of inhaled insulin was 15% vs. SC regular insulin (48). In a randomized study of

**Table 2. Pulmonary insulin delivery devices and formulations currently in development**

<b>Product</b>	<b>Manufacturer</b>	<b>Description</b>
Aerodose®	Aerogen, Inc.	Breath-actuated multidose inhaler delivers liquid insulin to the systemic circulation (64)
AERx®	Aradigm Corporation	Insulin diabetes management system (iDMS) creates aerosols (particles 1–3 µm in diameter) from liquid insulin. Uses microprocessors to guide patients visually to the correct rate and depth of breathing to administer insulin at the optimum moment in the inspiration-expiration cycle (50,51,63)
AIR®	Alkermes, Inc.	Uses particles formulated with a low mass, porous structure, 10–20 µm in diameter, to deliver relatively large drug particles from an inhaler device (61,62)
Exubera®	Nektar Therapeutics	Delivers a fine dry powder formulation (<5 µm in diameter) of regular short-acting human insulin to the deep lung in a reproducible and efficient manner (10,15,49)
Spiros®	Elan Pharmaceuticals, Inc.	Delivers a dry powder formulation through a handheld, battery-powered, multidose system (61)
Technosphere™/insulin	Pharmaceutical Discovery Corporation	The ordered lattice array of Technosphere dry powder microparticles and recombinant human insulin offers rapid onset of metabolic effect in a dose-dependent manner, with a short duration of action and low within-subject variability (65–67)

16 insulin-naïve subjects with type 2 diabetes, Gelfand and colleagues compared the PK profile and PPG control of inhaled insulin with that of SC insulin and found no significant differences in the reduction of postprandial hyperglycemia between the 2 groups (49). The reproducibility of inhaled insulin appeared comparable to that of injected insulin. However, inhaled insulin produced a more rapid peak and fall of plasma insulin levels compared to SC insulin.

### Clinical studies

Table 2 lists the devices that have recently been evaluated or are currently undergoing evaluation for the pulmonary delivery of insulin (10,15,49-67). All have shown promise in early clinical trials. In a study of 20 subjects with type 1 diabetes, 45 units of preprandial insulin delivered using the AERx<sup>®</sup> insulin diabetes management system (iDMS) were absorbed rapidly and showed a similar PD profile to that of 8 units of SC regular insulin given 30 minutes before a meal (50). The results of a study in healthy subjects suggested that changes in the inhaled volume and the depth of inspiration influenced the PK profile of insulin delivered using this system (51).

Evaluation of the Aerodose<sup>®</sup> Inhaler in 13 healthy subjects suggested that aerosolization time, but not particle size, had a significant impact on the metabolic effect of insulin delivered using this device (52). In a study of 15 subjects with type 2 diabetes, insulin delivered using the Aerodose Inhaler demonstrated a shorter time to peak action than SC insulin, with comparable dosing reproducibility (53).

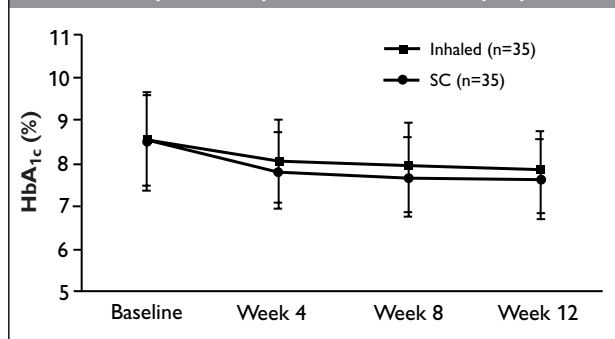
Exubera<sup>®</sup> appears to be the pulmonary delivery device that has advanced the furthest in clinical testing to date. In a randomized, 12-week study of 73 subjects with type 1 diabetes, changes in HbA<sub>1c</sub>, fasting blood glucose (FBG) and PPG concentrations, and the occurrence and severity of hypoglycemia were indistinguishable between the group of

patients treated with inhaled insulin and the control group treated with their usual insulin regimen (Figure 4) (10). This pulmonary device has also been evaluated in patients with type 2 diabetes. A randomized, 3-month study of subjects with type 2 diabetes on a stable insulin schedule showed that inhaled insulin significantly improved glycemic control compared to baseline, with a decrease in HbA<sub>1c</sub> of  $0.71 \pm 0.72\%$  (Figure 5) (54). Although not a direct comparison of inhaled and SC regular insulin, the effect of adding inhaled insulin to oral antihyperglycemic agents was evaluated in a randomized, 12-week study in 69 subjects with poorly controlled type 2 diabetes. HbA<sub>1c</sub> values decreased by  $>2\%$  in the group of patients treated with combination therapy, whereas no change in HbA<sub>1c</sub> from baseline was observed in the group randomized to oral antihyperglycemic agents alone (55). Lung function, assessed in full pulmonary function studies, remained stable for the duration of these short-term trials (10,54,55).

In consideration of the importance of patient compliance with insulin therapy, a significant observation of these studies was that patients rated inhaled insulin (Exubera) higher than SC insulin in terms of ease of administration, comfort, convenience and overall satisfaction. Subjects completed satisfaction questionnaires; 82% of those patients with type 1 diabetes and 92% with type 2 diabetes receiving inhaled insulin opted to enter into an extension phase of the trials. Subjects who switched from SC to inhaled insulin noted significant improvement in global satisfaction, ease of use and convenience. Conversely, subjects who switched from inhaled to SC insulin showed a trend toward worsening satisfaction (56).

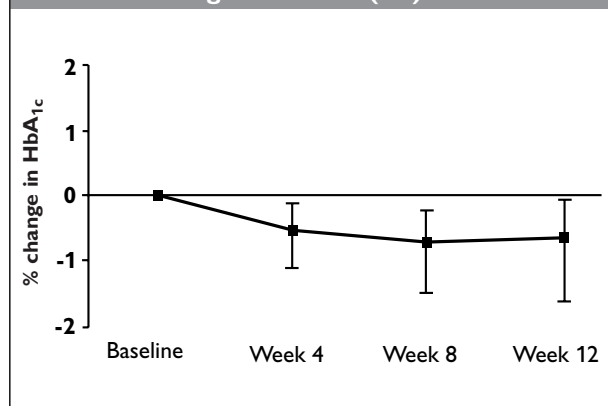
This trend for improved patient satisfaction and glycemic outcomes appears consistent with findings in the limited reports of phase III studies with Exubera. In a 6-month study of 334 subjects with type 1 diabetes, the HbA<sub>1c</sub> values of subjects who received inhaled insulin and a single bedtime injection of Ultralente insulin were comparable to those of

**Figure 4. Average HbA<sub>1c</sub> over a 12-week period in patients with type 1 diabetes, comparing Exubera<sup>®</sup> (inhaled) vs. SC insulin (10)**



Data are mean $\pm$ SD  
SC = subcutaneous  
SD = standard deviation

**Figure 5. Percent change in HbA<sub>1c</sub> levels in patients with type 2 diabetes using Exubera<sup>®</sup> (54)**



Error bars represent 1 SD  
SD = standard deviation

subjects treated with conventional insulin therapy. However, subjects receiving inhaled insulin reported enhanced satisfaction, quality of life and acceptance of IIT (57,58). Furthermore, in a study of 309 subjects with type 2 diabetes who were poorly controlled with oral antihyperglycemic therapy, glycemic control (as assessed by HbA<sub>1c</sub>) improved by 1.4% in subjects who received inhaled insulin alone and by 1.9% in those who received inhaled insulin in combination with oral agents, compared to the small 0.2% reduction in HbA<sub>1c</sub> in those treated with oral agents alone (59). In terms of patient satisfaction, the 2 groups using inhaled insulin preferred the inhaled insulin over their previous regimens (60).

### Side effects and contraindications

In phase III studies, the frequency and nature of adverse events were comparable between Exubera- and SC insulin-treated groups, with symptoms of hypoglycemia reported as the most common adverse event in both treatment arms (58). The most common respiratory side effect reported among patients using Exubera was cough, characterized as mild to moderate in nature. Pulmonary function tests in the phase II studies were comparable between the groups (10,54,55). The efficacy and safety of inhaled insulin in patients with chronic obstructive pulmonary disease (COPD) or emphysema, or in chronic smokers, has not been determined in the studies discussed above. Evaluation of pulmonary function over the long term is ongoing.

### SUMMARY

The search for a feasible and clinically applicable noninvasive insulin delivery system has recently received considerable research interest. Several delivery systems appear to have overcome many of the physiological and anatomical barriers that have limited successful implementation of past research approaches. Whether noninvasive insulin delivery can overcome or reduce the frequency of other concerns of IIT (e.g. hypoglycemia) still requires evaluation. Given the recent success of several systems currently undergoing evaluation, it is conceivable that noninvasive insulin delivery will become a clinical reality in the near future.

### REFERENCES

1. Birkeland KI. Improving glycaemic control with current therapies. *Diabet Med.* 1998;15(suppl 4):S13-S19.
2. Chehade JM, Mooradian AD. A rational approach to drug therapy of type 2 diabetes mellitus. *Drugs.* 2000;60:95-113.
3. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med.* 1999;131:281-303.
4. Riddle M. Combining sulfonylureas and other oral agents. *Am J Med.* 2000;108(suppl 6a):15S-22S.
5. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA.* 1999;281:2005-2012.
6. Berger M, Jörgens V, Mühlhauser I. Rationale for the use of insulin therapy alone as the pharmacological treatment of type 2 diabetes. *Diabetes Care.* 1999;22(suppl 3):C71-C75.
7. European Diabetes Policy Group 1999. A desktop guide to type 2 diabetes mellitus. *Diabet Med.* 1999;16:716-730.
8. National Institute of Diabetes and Digestive and Kidney Diseases. *National Diabetes Statistics Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2000.* Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health; 2002. Publication 02-3892.
9. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993; 329:977-986.
10. Skyler JS, Cefalu WT, Kourides IA, et al. Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomised proof-of-concept study. *Lancet.* 2001;357:331-335.
11. Zambanini A, Newson RB, Maisey M, Feher MD. Injection related anxiety in insulin-treated diabetes. *Diabetes Res Clin Pract.* 1999;46:239-246.
12. Wallace TM, Matthews DR. Poor glycaemic control in type 2 diabetes: a conspiracy of disease, suboptimal therapy and attitude. *Q J M.* 2000;93:369-374.
13. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352:837-853.
14. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ.* 1997; 314:1512-1515.
15. Cefalu WT, Skyler JS, Kourides IA, et al. Inhaled human insulin treatment in patients with type 2 diabetes mellitus. *Ann Intern Med.* 2001;134:203-207.
16. Woodworth JR, Howey DC, Bowsher RR. Establishment of time-action profiles for regular and NPH insulin using pharmacodynamic modeling. *Diabetes Care.* 1994;17:64-69.
17. Bruttomesso D, Pianta A, Mari A, et al. Restoration of early rise in plasma insulin levels improves the glucose tolerance of type 2 diabetic patients. *Diabetes.* 1999;48:99-105.
18. Polonsky KS, Given BD, Hirsch LJ, et al. Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. *N Engl J Med.* 1988;318:1231-1239.
19. Mudaliar SR, Lindberg FA, Joyce M, et al. Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin. Absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. *Diabetes Care.* 1999;22:1501-1506.
20. Heinemann L, Heise T, Wahl LC, et al. Prandial glycaemia after a carbohydrate-rich meal in type I diabetic patients: using the rapid acting insulin analogue [Lys(B28), Pro(B29)] human insulin. *Diabet Med.* 1996;13:625-629.

21. Saudek CD. Novel forms of insulin delivery. *Endocrinol Metab Clin North Am.* 1997;26:599-610.
22. Bohannon NJV. Insulin delivery using pen devices. Simple-to-use tools may help young and old alike. *Postgrad Med.* 1999;106:57-68.
23. Blundell TL, Dodson GG, Hodgkin D, Mercola DA. Insulin: the structure in the crystal and its reflection in chemistry and biology. *Adv Protein Chem.* 1972;26:279.
24. Golden MP, Haymond M, Hinnen DA, et al. Position statement on jet injectors. *Diabetes Care.* 1988;11:600-601.
25. Kanikkannan N, Singh J, Ramarao P. Transdermal iontophoretic delivery of bovine insulin and monomeric human insulin analogue. *J Control Release.* 1999;59:99-105.
26. Mitragotri S, Blankschtein D, Langer R. Ultrasound-mediated transdermal protein delivery. *Science.* 1995;269:850-853.
27. Cevc G, Gebauer D, Stieber J, et al. Ultraflexible vesicles, transfersomes, have an extremely low pore penetration resistance and transport therapeutic amounts of insulin across the intact mammalian skin. *Biochim Biophys Acta.* 1998;1368:201-215.
28. Major RH. The intranasal application of insulin. *J Lab Clin Med.* 1935;21:278-280.
29. Hilsted J, Madsbad S, Hvidberg A, et al. Intranasal insulin therapy: the clinical realities. *Diabetologia.* 1995;38:680-684.
30. Coates PA, Ismail IS, Luzio SD, et al. Intranasal insulin: the effects of three dose regimens on postprandial glycaemic profiles in type II diabetic subjects. *Diabet Med.* 1995;12:235-239.
31. Jacobs MA, Schreuder RH, Jap-A-Joe K, et al. The pharmacodynamics and activity of intranasally administered insulin in healthy male volunteers. *Diabetes.* 1993;42:1649-1655.
32. Lalej-Bennis D, Boillot J, Bardin C, et al. Efficacy and tolerance of intranasal insulin administered during 4 months in severely hyperglycaemic type 2 diabetic patients with oral drug failure: a cross-over study. *Diabet Med.* 2001;18:614-618.
33. Hoffman A, Ziv E. Pharmacokinetic considerations of new insulin formulations and routes of administration. *Clin Pharmacokinet.* 1997;33:285-301.
34. Chetty DJ, Chien YW. Novel methods of insulin delivery: an update. *Crit Rev Ther Drug Carrier Syst.* 1998;15:629-670.
35. Davis SS. Overcoming barriers to the oral administration of peptide drugs. *Trends Pharmacol Sci.* 1990;11:353-355.
36. Ramdas M, Dileep KJ, Anitha Y, et al. Alginate encapsulated bioadhesive chitosan microspheres for intestinal drug delivery. *J Biomater Appl.* 1999;13:290-296.
37. Still JG. Development of oral insulin: progress and current status. *Diabetes Metab Res Rev.* 2002;18(suppl 1):S29-S37.
38. Abbas R, Leone-Bay A, Agawal RK, et al. Oral insulin: pharmacokinetics and pharmacodynamics of human insulin following oral administration of an insulin/delivery agent capsule in healthy volunteers [abstract]. *Diabetes.* 2002;51(suppl 2):A48. Abstract 197-OR.
39. Sayani AP, Chien YW. Systemic delivery of peptides and proteins across absorptive mucosae. *Crit Rev Ther Drug Carrier Syst.* 1996;13:85-184.
40. Levin P, Yutzky P, Chez N, et al. Improved post-prandial glucose control with OralIn at breakfast, lunch and dinnertime [abstract]. *Diabetes.* 2001;50(suppl 2):A124. Abstract 497-P.
41. Modi P, Mihic M. Replacement of s.c. injections with OralIn in treatment of diabetes [abstract]. *Diabetes.* 2001;50(suppl 2):A44. Abstract 179-OR.
42. Pozzilli P, Modi P, Manfrini S, et al. Pharmacokinetics of oral spray insulin vs. regular insulin and lispro insulin in type-1 diabetes [abstract]. *Diabetes.* 2002;51(suppl 2):A48. Abstract 196-OR.
43. Modi P, Guevara-Aguirre J, Guevara M, et al. Oral insulin spray (Oralin) as meal insulin for treatment of type 1 diabetes. *Diabetologia.* 2002;45(suppl 2):A17.
44. Gäansslen M. Über inhalation von insulin. *Klin Wochenschr.* 1925;4:71.
45. Wigley FW, Londono JH, Wood SH, et al. Insulin across respiratory mucosae by aerosol delivery. *Diabetes.* 1971;20:552-556.
46. Heinemann L, Traut T, Heise T. Time-action profile of inhaled insulin. *Diabet Med.* 1997;14:63-72.
47. Heise T, Rave K, Bott S, et al. Time-action profile of an inhaled insulin preparation in comparison to insulin lispro and regular insulin [abstract]. *Diabetes.* 2000;49(suppl 1):A10. Abstract 39-OR.
48. Laube BL, Benedict GW, Dobs AS. Time to peak insulin level, relative bioavailability, and effect of site of deposition of nebulized insulin in patients with noninsulin-dependent diabetes mellitus. *J Aerosol Med.* 1998;11:153-173.
49. Gelfand RA, Schwartz SL, Horton M, et al. Pharmacological reproducibility of inhaled human insulin pre-meal dosing in patients with type 2 diabetes mellitus (NIDDM) [abstract]. *Diabetes.* 1998;47(suppl 1):A99. Abstract 0388.
50. Kipnes M, Otulana B, Okikawa J, et al. Pharmacokinetics and pharmacodynamics of pulmonary insulin delivered via the AERx<sup>®</sup> diabetes management system in type 1 diabetics [abstract]. *Diabetologia.* 2000;43:A202.
51. Farr SJ, McElduff A, Mather LE, et al. Pulmonary insulin administration using the AERx<sup>®</sup> system: physiological and physicochemical factors influencing insulin effectiveness in healthy fasting subjects. *Diabetes Technol Ther.* 2000;2:185-197.
52. Heinemann L, Kapitza C, Heise T, et al. Impact of particle size and aerosolisation time on the metabolic effect of an inhaled insulin aerosol [abstract]. *Diabetologia.* 2001;44:A5. Abstract 10.
53. Perera AD, Kapitza C, Nosek L, et al. Reproducibility of inhaled and subcutaneous insulin in type 2 diabetic patients [abstract]. *Diabetologia.* 2001;44:A212. Abstract 815.
54. Cefalu WT, Gelfand RA, Kourides I. Treatment of type 2 diabetes mellitus with inhaled human insulin: a 3-month, multicenter trial [abstract]. *Diabetes.* 1998;47(suppl 1):A61. Abstract 0237.
55. Weiss SR, Berger S, Cheng S-L, et al. Adjunctive therapy with inhaled human insulin in type 2 diabetic patients failing oral agents: a multicenter phase II trial [abstract]. *Diabetes.* 1999;48(suppl 1):A12. Abstract 0048.
56. Gerber RA, Cappelleri JC, Bell-Farrow AD, et al. Improved patient satisfaction with inhaled insulin in subjects with type 1 diabetes mellitus after one year: results from a multicenter

- extension trial [abstract]. *Diabetes*. 2000;49(suppl 1):A108. Abstract 436-P.
57. Testa MA, Turner RR, Hayes JF, et al. Patient satisfaction and quality of life in type 1 diabetes: a randomized trial of injectable vs inhaled insulin [abstract]. *Diabetes*. 2001;50(suppl 2):A45. Abstract 182-OR.
58. Skyler JS. Efficacy and safety of inhaled insulin (Exubera<sup>®</sup>) compared to subcutaneous insulin therapy in an intensive insulin regimen in patients with type 1 diabetes: results of a 6-month, randomized, comparative trial [abstract]. *Diabetes*. 2002;51(suppl 2):A134. Abstract 540-P.
59. Rosenstock J. Mealtime rapid-acting inhaled insulin (Exubera<sup>®</sup>) improves glycemic control in patients with type 2 diabetes failing combination oral agents: a 3-month, randomized, comparative trial [abstract]. *Diabetes*. 2002;51(suppl 2):A132. Abstract 535-P.
60. Simonson DC, Hayes JF, Turner RR, et al. Treatment satisfaction and preferences in type 2 diabetes: a randomized trial of oral agents vs inhaled insulin [abstract]. *Diabetes*. 2001;50(suppl 2):A131. Abstract 528-P.
61. Greener MJ. Leading applications of inhaled delivery systems for systemically active drugs. *Spectrum Drug Deliv Reform Technol*. 2000;2:1-16.
62. Hrkach J, Batycky R, Chen D, et al. AIR insulin: complete diabetes therapy via inhalation of fast-acting and slow-acting dry powder aerosols [abstract]. *Diabetes*. 2000;49:A9. Abstract 37-OR.
63. Balent B, Brunner GA, Sendlhofer G, et al. Dose-response and system efficiency of pulmonary insulin in subjects with type 1 diabetes [abstract]. *Diabetologia*. 2000;43:A202.
64. Fishman RS, Guinta D, Chambers F, et al. Insulin administration via the Aerodose inhaler: comparison to subcutaneously injected insulin [abstract]. *Diabetes*. 2000;49:A9. Abstract 38-OR.
65. Kapitza C, Heise T, Pfützner A, et al. Dose-response characteristics for a new pulmonary insulin formulation and inhaler [abstract]. *Diabetologia*. 2000;43:A46.
66. Pfützner A, Heise T, Steiner S, et al. Inhaled Technosphere/insulin shows a low variability in metabolic action in type 2 diabetic patients [abstract]. *Diabetes*. 2000;49:A121. Abstract 492-P.
67. Pfützner A, Rave K, Heise T, et al. Low variability in metabolic action in type 2 diabetic patients with inhaled Technosphere<sup>TM</sup>/insulin [abstract]. *Diabetologia*. 2000;43:A202.