

Future options for insulin therapy

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The epoch-making discovery of insulin in 1921 was a miracle of 20th century medicine. Over the ensuing 80 years there has been a reliance on subcutaneous injections as the main route of administration. Therefore, ever since its introduction, countless attempts have been made to utilize less intrusive means of giving insulin long term. Little or no success has been achieved with the oral, buccal, dermal, nasal and rectal routes of delivery. However, efforts are continuing with the concomitant use of various absorption enhancers, encapsulating insulin within liposomes or microcapsules, using muco-adhesive materials and/or modification of the insulin molecule itself. Combination strategies are undoubtedly necessary to improve bioavailability. In contrast, utilizing the pulmonary route has been shown to achieve comparable efficacy to subcutaneous soluble insulin in providing mealtime insulin supplementation. However, the bioavailability of inhaled insulin, both liquid and powder formulations, remain relatively low at approximately 20% compared to subcutaneous insulin. Patient satisfaction

has been high for this route of delivery. Currently, long-term pulmonary safety is a major issue being actively addressed. This route could therefore possibly represent the first real alternative to subcutaneous injections. Important developments have also occurred since the mid 1970s in insulin pump therapy with the more recent advent of smaller and safer external and implantable pumps. The availability of better external and internal glucose sensors is facilitating the move towards 'closed-loop' systems. Year-long data in man is now beginning to appear with implantable devices connected to a glucose sensor sited intravenously. Considerable work is also underway in an effort to better utilize islet cells and stem cells, thus obviating the need for the administration of exogenous insulin. There is therefore cautious optimism in this new millennium for our insulin-requiring patients in a number of aspects relating to both alternative routes of insulin administration and the possibility of independence from exogenous insulin in the longer term.

SINCE the introduction of subcutaneous insulin therapy into clinical practice in the 1920s (ref. 1), numerous developments in the production, purification, formulation and administration of insulin have delivered improved glycemic control for patients with diabetes. However, the continued existence of diabetes-related complications illustrates the difficulty in achieving and maintaining near-normoglycemia with existing treatment regimens². The pharmacokinetics of 'conventional' insulin preparations given by bolus subcutaneous injection make it virtually impossible to replicate the normal pattern of nutrient-related and basal insulin secretion. Many factors are known to contribute to the high inter- and intra-subject variability in subcutaneous absorption³ (Table 1). The advent of recombinant DNA technology provided an opportunity to 'design' insulin analogues in an attempt to overcome some of these limitations⁴. The subsequent availability of 'rapid-acting' (insulin lispro, insulin aspart) and 'long-acting' (insulin glargine, detemir insulin) insulin analogues for meal and basal requirements offer both individual and collective advantages⁴⁻⁶.

A recognition of the need for multiple daily injections as part of intensive insulin regimens led to the introduction of pen injectors in the 1980s (ref. 7). Parallel developments in subcutaneous insulin delivery has led to external continuous subcutaneous insulin infusion (CSII) pumps^{8,9} capable of achieving excellent metabolic control with reduced risk of hypoglycemia¹⁰⁻¹³. Implantable insulin pumps (IIP) have also been in development^{14,15}. Ultimately, the goal of this technology is to develop miniature external or implantable closed loop systems incorporating a glucose sensor to allow automatic infusion of insulin in response to metabolic needs.

As an alternative strategy, countless attempts have been made over the years to explore the potential of virtually every less invasive route for insulin administration^{16,17}. Feasibility studies, mostly based on animal models, have been disappointing due to low and inconsistent bioavailability and a requirement for high doses of insulin and the concomitant use of absorption enhancers. The much fewer studies in humans have concentrated on the oral, buccal, rectal, dermal, nasal and pulmonary routes of delivery. Success has again been limited, although the intrapulmonary route is receiving renewed

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attention at present. In this article, we review the status of the alternative routes for insulin delivery.

Peroral delivery

Attempts to develop methods for the oral administration of insulin have met with little, if any, success¹⁸ despite the use of numerous strategies to overcome the barriers to absorption presented by the gastrointestinal tract¹⁹. Improving the chemical stability of insulin, protecting against proteolytic enzymes and increasing permeability of the intestinal mucosa have all been tried²⁰. Incorporating insulin into 'liposomes' to reduce both enzymatic degradation and enhance absorption has also been extensively investigated²¹ as well as encapsulation into enteric coated, biodegradable polymer nano- or microspheres^{19,22}. Unfortunately, the highly variable transit time through the gastrointestinal tract, combined with very low bioavailability, make this route not only highly impracticable but also economically unattractive at present.

Orally administered insulin may, however, be of prophylactic value by enhancing immune tolerance in individuals at high risk of developing Type 1 diabetes²³. Whilst, studies to date²⁴ suggest little or no benefit, a similar strategy is under evaluation in the Diabetes Prevention Trial (DPT-1).

Buccal/sublingual delivery

Although easily accessible, the buccal and sublingual mucosae present special problems for insulin delivery due to the combined effects of a relatively thick multi-layered buccal barrier and the constant flow of saliva. In animal studies, the concomitant use of absorption

enhancers alone, or in combination with a bio-adhesive delivery system, reduced blood glucose of up to 30% relative to intramuscular insulin, but lacked reproducibility^{25,26}.

Oralin, a liquid insulin aerosol formulation of mixed micelles made from a combination of absorption enhancers, sprayed into the mouth using a pressurized aerosol, is currently being investigated in patients with Type 2 diabetes²⁷⁻²⁹. However, at this time, pharmacokinetic data is limited and no studies relating to safety or efficacy have been published.

Rectal delivery

About 70% of rectally administered insulin enters the systemic circulation via the lymphatic system circumventing hepatic extraction that occurs by other routes³⁰. However, absorption from the rectum is poor and inconsistent and thus requires the incorporation of enhancers into suppositories or gels^{16,17}. Bioavailability in humans remains very low (4–10%) and appears not to be dose related³¹⁻³³. Compared to subcutaneous injection, rectally delivered insulin acts more rapidly and is shorter-lived. Whereas improvement in short-term glycaemic control over a 30-day period has been demonstrated³³, long-term acceptance of this route of delivery is unlikely.

Transdermal delivery

Although the skin is easily accessible and has a large surface area (about one square meter), it is relatively impermeable to large hydrophilic polypeptides such as insulin. Several methods have been employed to improve transdermal transfer including iontophoresis³⁴⁻³⁷, low frequency ultrasound (phonophoresis)^{38,39} and drug carrier agents such as transfersomes⁴⁰. Transport of hexameric insulin by iontophoresis across mouse skin is poor, but smaller, monomeric sulfated insulin and insulin analogues with increased negative charge are transferred more efficiently, although still at a rate barely supporting basal insulin requirements³⁷. A pulsed transdermal iontophoretic system appears more effective than conventional direct current.

Insulin maybe transported across the skin with a relatively high degree of efficiency (≥ 50 percent) when incorporated into lipid-based transfersomes (a phosphatidylcholine-based drug carrier)⁴⁰. When applied (30 units) to intact human skin, plasma glucose was reduced by about 20% within 3–4 h and lasting 10 h or more. Despite these initial, encouraging observations, no further information has been forthcoming. Whereas success to date has been lacking, combining physical and chemical technologies maybe a better option, although the prospect remains doubtful.

Table 1. Factors influencing the pharmacokinetics of subcutaneously injected insulin

• Pharmaceutical formulation:
Species, concentration, additives
Solution, suspension
• Injection conditions:
Site and depth of injection
Volume and dose
Delivery device
Body posture
• Miscellaneous:
Exercise
Massage
Temperature (ambient and body temperature)
Smoking
? Blood glucose
(adapted from Brange <i>et al.</i> ³)

Intranasal delivery

The nasal mucosa provides a relatively large surface area for absorption (about 150 cm² in humans) with a rich vascular subepithelium and lymphatic system. Local barriers to insulin absorption include a mucociliary transport mechanism with an enzymatically active and low permeability nasal epithelium.

Clinical experience has demonstrated that the pharmacokinetic profile of nasally administered insulin resembles intravenous insulin but that despite the use of various enhancers bioavailability rarely exceeds 20% (refs 40–44). Short-term studies in patients with Type 2 diabetes found that nasally administered insulin produced a rapid but short-lived hypoglycemic effect⁴⁵ which failed to adequately control post-prandial glycemia without very high doses^{46–48}. In longer term studies (1–4 months) in patients with Type 1 diabetes, the relatively short-lived effect of pre-prandial intranasal insulin was confirmed^{49–51} necessitating an increased dose of basal insulin⁴⁷. Discontinuation of nasal insulin due to deteriorating metabolic control occurred in approximately 20% of patients⁵¹. Local irritation and disruption or damage to the nasal mucosa and nasociliary function is also a disturbing feature.

The limited clinical efficacy of intranasal insulin in controlling meal-related glucose excursions requiring high doses and repeated administrations, combined with acute and/or long-term adverse tolerability have led to its discontinuation⁴⁷.

Intrapulmonary route

The respiratory tree offers the largest available surface area for drug delivery (around 140 sq m in humans). Unlike the epithelia of the gastrointestinal tract and nose, the very thin (0.1–0.2 µm), highly permeable and richly vascularized alveolar surface ('deep lung') provides an attractive option for the systemic delivery of drugs and polypeptide hormones^{52–54}. The absorption of polypeptides larger than 40 kDa is thought to occur by transcytosis, with smaller molecules, including insulin, absorbed by paracellular mechanisms^{54,55}. The immunotolerant nature of the lung to self-proteins is also of considerable advantage in this context⁵⁴.

The first attempts at intrapulmonary delivery were made in the 1920s (refs 56, 57). However, almost 50 years elapsed before the feasibility of inhaled aerosolized liquid insulin was demonstrated⁵⁸. Initial observations were soon confirmed by others revealing a more rapid absorption and clearance compared to subcutaneous administered insulin⁵⁹. Glycemic control comparable to subcutaneous insulin was demonstrated in a small number of children over a 3-day period by nebulizing neutral, soluble insulin at 4 to 5 times the normal subcutaneous

dose⁶⁰. Scintigraphy revealed that 50–93% of the aerosolized insulin is deposited below the larynx⁶¹. Crude estimates of bioavailability in non-smokers ranged between 7 and 25% (refs 61–64), with three-fold higher values seen in smokers⁶⁵. The variability in the blood glucose response appears equivalent to that seen for the subcutaneous route^{59,66,67}.

Many factors influence the amount and the site of deposition of inhaled insulin in the pulmonary tree (Table 2)^{68–70}. These include particle size or 'aerodynamic diameter' (a function of the particle's geometric diameter and mass density), surface morphology, charge, solubility, hygroscopicity and, less importantly, formulation, pH and concentration. Other influences on pulmonary drug delivery and absorption include not only the emitted dose and its dispersability (respirable fraction), but the pattern of breathing^{69,70}, airflow obstruction, interstitial lung disease⁷¹, smoking^{72,73} and exercise⁷⁴. Deposition in the lung periphery (alveolar or 'deep lung') is optimal for aerosol particles with a mean aerodynamic diameter of 1–3 µm⁷⁵. Larger particles of 5–10 µm and > 10 µm are predominantly deposited in the tracheobronchial ('central lung') or oropharyngeal regions respectively with the smallest particles (< 1 µm) being mostly exhaled⁷⁶ (Figure 1).

Traditional aerosol devices for inhalation therapy include portable, pressurized-metered dose inhalers (pMDI), dry powder inhalers (DPI) and a wide range of stationary nebulizers⁷⁷. All inhalers produce a polydisperse aerosol characterized by the mass median aerodynamic diameter (MMAD) and the particle size range (geometric standard deviation, GSD) which, along with the mass output (particle mass and numbers per volume), are initial critical factors in the pulmonary delivery of insulin. MDI and DPI systems are flow rate-dependent and therefore subject to large inter- and intra-subject variability and low deep lung deposition^{78–80}. Delivery of the insulin aerosol at the beginning of a slow, inspiratory flow rate coupled with a large tidal volume optimises

Table 2. 'Conventional' aerosol delivery systems – factors able to influence amount and site of deposition of inhaled insulin in the pulmonary tree

<ul style="list-style-type: none"> • Delivered dose • Particle or droplet – size, density, mass – dispersion (Median Mass Aerodynamic Diameter, Geometric Standard Deviation) • Humidity • Moment of aerosol actuation • Inspiratory flow • Inhaled volume • Airways disease • Breath-hold, cough • Smoking • Exercise • Interstitial lung disease • Patient type: child, adult • Education, technique, compliance

'deep-lung' deposition^{69,70}. The performance of the delivery device and control over breathing are, therefore, pivotal in achieving a desired and reproducible effect. In addition, the patient's acceptance and ability to operate the inhaler devices is key in determining their overall efficiency⁸¹.

To date, most clinical experience has been obtained using a dry powder insulin formulation in the Inhale device (Inhale Therapeutic Systems, Pfizer Inc., Aventis Pharma) or a liquid aerosol formulation in the AERx[®] iDMS (Aradigm Corp, Novo Nordisk) device (Figure 2, Table 3).

When using the dry powder insulin formulation in the inhale device, a respirable aerosol 'cloud' of insulin is captured in a holding 'spacing chamber' and then inhaled at the beginning of a series of deep breaths. The holding chamber allows discrete, slow, deep inhalations. The overall efficiency (a product of aerosolization losses and bioavailability) using this device in non-smokers is approximately 10% in healthy subjects and 11–13% in patients with Type 2 diabetes compared to soluble human insulin^{81,82}. Two formulations (1 mg and 3 mg) are available which have similar pharmacokinetic time course profiles and show a dose-related increase in serum insulin concentration. The mean bioavailability of the 1 ($\times 3$) and 3 mg ($\times 1$) formulations, relative to 0.15 U/kg soluble insulin given subcutaneously, were equivalent at 9 and 8.4% respectively with similar levels of intra-subject variability (approximately 40%). The dry powder inhaled insulin formulation achieves a faster onset of action than subcutaneous soluble insulin with a time to peak effect resembling the fast-acting insulin analogue, insulin lispro, and an offset of action from 5–10 h that is intermediate between lispro insulin and soluble insulin (Figure 3)⁸¹. The bioactivity of 1mg of the inhaled insulin is considered equivalent to 3U of subcutaneous soluble human insulin with a relative biopotency estimated at approximately 10 and 11% compared to subcutaneous soluble insulin and insulin lispro respectively. Pharmacokinetic and pharmacodynamic studies demonstrate comparable reproducibility to subcutaneous insulin⁸².

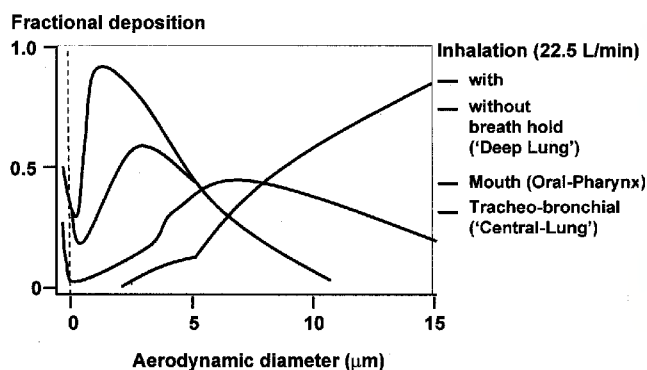


Figure 1. Intra-pulmonary delivery of insulin, influence of particle size, inspiratory flow rate and inhaled volume on particle deposition as a function of aerodynamic diameter. Adapted from ref. 76.

In a 'proof of concept' study of 70 patients with Type 1 diabetes, inhaled insulin, given immediately before meals with ultralente insulin at bedtime, was compared with a control group on a conventional split-mixed subcutaneous insulin regimen comprising 2 or 3 injections of soluble and NPH insulin⁸³. At the end of a 3-month treatment period, the inhaled insulin group achieved a slightly lesser reduction in HbA_{1c} compared to the control group for total daily insulin doses of 61U (estimated) and 47U respectively. These results imply a bio-equivalence for inhaled insulin of around 8% of subcutaneous insulin. The frequency of hypoglycemia was similar in both treatment groups and no significant differences in pulmonary function tests occurred, with 82% of patients electing to remain on inhaled insulin.

In a further 3-month uncontrolled study, 26 insulin treated patients with Type 2 diabetes on a poorly-defined subcutaneous insulin regimen were converted to inhaled insulin before each meal with ultralente insulin at bedtime⁸⁴. A meal test, in which subcutaneous or inhaled insulin was given 30 and 10 min respectively prior to eating, was carried out pre-conversion and after 12 weeks. A small improvement of 0.71% in mean HbA_{1c} over the study period was seen with no difference observed in post-prandial glycemia during the standardized meal test. Results from the 'control' group were not included. Pulmonary function tests remained essentially unchanged. Both uncontrolled studies are able only to demonstrate the feasibility of intrapulmonary insulin delivery. Neither of these two studies reported on the presence of insulin-binding antibodies.

The AERx[®] iDMS combines single-use strips containing a liquid insulin formulation, equivalent to 10U of soluble insulin by subcutaneous injection, in a breath-activated, microprocessor controlled device (Figure 2), designed to minimize variability due to patient technique⁷⁰. The liquid aerosol insulin generated by the device is released early in inspiration and then only when



Figure 2. Examples of pulmonary insulin delivery devices, *a*, Inhale Therapeutic Systems – Pfizer Inc. and Aventis Pharma; Exubera[™]; *b*, Aradigm Corp. and Novo Nordisk A/S; AERx[®] iDMS.

the inspiratory flow rate and inhaled volume are optimal. Ensuring a combination of slow inspiration and early delivery of aerosol results not only in improved 'deep lung' deposition but reduced within and between subject variability, comparable to subcutaneous injection⁷⁰. In a dose-response study of 18 patients with Type 1 diabetes, a near linear relationship for both pharmacokinetic (Figure 4) and pharmacodynamic parameters was observed with inhaled soluble human insulin for the 0.3 to 1.8 U/kg range over a 10-hour period⁸⁵. The insulin aerosol was generated by the delivery system only when the inspiratory flow rate was within 50–70 l per min. After inhalation, patients were instructed to hold their breath for 10 seconds and then to exhale slowly. In comparison soluble human insulin was given by subcutaneous injection at a dose of 0.12 U per kg. Plasma glucose was kept constant by a variable infusion of glucose ('glucose clamp') after each insulin administration. Only at the higher doses (1.2 and 1.8 U per kg), was insulin inhaled more rapidly in onset of action than subcutaneous insulin. The calculated pharmacodynamic system efficiency of inhaled insulin was 12.7%.

Insulin, administered just prior to a test meal using the AERx[®] iDMS, achieves a similar impact on the postprandial glucose excursion as subcutaneous soluble insulin injected 30 min before eating⁸⁶. The calculated pharmacokinetic and pharmacodynamic system efficiencies of the inhaled insulin were 16 and 17% respectively. Delivering the rapid-acting insulin analogue, insulin lispro, by inhalation results in peak plasma insulin concentrations much earlier than with subcutaneous injection⁸⁷.

Scintigraphic studies comparing the conventional pressurized MDI and an early prototype of the AERx[®] system demonstrated a predominantly central pattern of distribution with the MDI device compared to a more homogeneous pattern with the AERx[®] system⁸⁸. Although the

emitted dose was similar for the MDI and AERx[®] delivery devices (63 and 61% respectively), the amount of aerosolized droplets <5.7 µm was less for the solution MDI (71% versus 91%) contributing to a lower (22% versus 53%) and more variable deep lung distribution. Deposition in the oro-pharyngeal region was also largely avoided emphasizing the importance of minimizing the ballistic component associated with pressurized MDIs.

Technical differences between the Inhale (Exubera[™]) and AERx[®] delivery systems are not translated into major differences in bioavailability or relative bioeffectiveness. Cytosolic bio-degradation appears to be the greatest factor contributing to low bioavailability of inhaled insulin. The use of liquid insulin formulations avoids difficulties associated with the production of insulin powders and the influence of external humidity on dispersion. However, dry powders may have better stability at room temperature.

Increased efficiency of aerosol formulations may be achieved by adjusting particle surface morphology and solubility to influence the pharmacokinetic and dynamic characteristics⁸⁹. Advanced Inhalation Research (AIR, Alkermes – Eli Lilly) have developed porous, dry aerosol particles of low mass density and large size which remain within the aerodynamic diameter window of 1–3 µm. Potential advantages include limiting the tendency of particles to aggregate and reducing susceptibility to phagocytosis⁸⁹. In addition to a fast-acting formulation, a sustained release of insulin can be achieved from large porous particles of protamine and/or zinc-insulin suspension reformulated as dry powders⁹⁰. These particles can be easily aerosolized using a simple breath-activated inhalation device.

In an attempt to further improve the bioavailability of inhaled insulin formulations, the effect of incorporating enhancers and/or proteolytic enzyme inhibitors has been examined⁹¹. Pharmaceutical Discovery Corporation (Elmsford, NY, USA) have developed a Technosphere[™]/insulin complex. This is a dry powder formulation containing diketopiperazine derivatives as the enhancer assembled in an ordered lattice array that dissolves at neutral pH on the alveolar surface releasing the insulin. In a small pilot study in non-smoking, normal subjects, the time to maximum plasma insulin concentration for the intravenous, intrapulmonary and subcutaneous routes were 5, 13 and 121 min respectively, returning to baseline after 60, 180 and 360 min respectively⁹². The bioavailability of the inhaled insulin relative to intravenous insulin was estimated at 14.6%. Compared to subcutaneous administration, the relative bioavailability of the inhaled insulin was calculated over an abbreviated period of 180 min, giving a falsely high value of 23%. In a dose-response, euglycemic clamp study in healthy subjects at 25, 50 and 100 IU of Technosphere[™]/insulin, the biopotency, relative to subcutaneous soluble human insulin given at a low dose of 10 IU and estimated over a 6 h

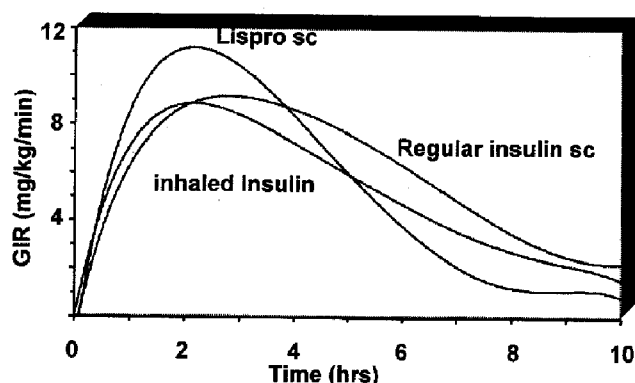


Figure 3. Time-action pharmacodynamic characteristics of inhaled insulin (dry powder formulation) using the Exubera[™] delivery device (Pfizer Inc. and Aventis Pharma). The glucose infusion rate (GIR) was estimated during an isoglycaemic glucose clamp. Inhaled insulin (6 mg ~ 168 units of insulin) was compared to subcutaneous regular (soluble human) insulin (16 units) and the rapid-acting insulin analogue, insulin lispro (16 units). Adapted from Heise *et al.*⁸¹.

Table 3. Devices for intrapulmonary delivery of insulin

Manufacturer	Name of device	Insulin formation	Breath activation	Size	Dose adjustment	Compliance monitor	Battery
Inhale Therapeutic Systems, Inc./Pfizer/Aventis	Inhance™/Exubera™	Dry powder	No	Large	Coarse	No	No
Aradigm/Novo Nordisk	AERx® iDMS	Liquid	Yes	Large	Fine	Yes	Yes
Alkermes/Eli Lilly	AIR	Dry powder	Yes	Small	Coarse	No	No
AeroGen/Becton Dickinson	AeroDose	Liquid	Yes	Small	Fine	No	Yes
Pharmaceutical Discovery Corporation, Elmsford, NY	MedTone™	Dry Powder–Technospheres™	No	Small	Coarse	No	No

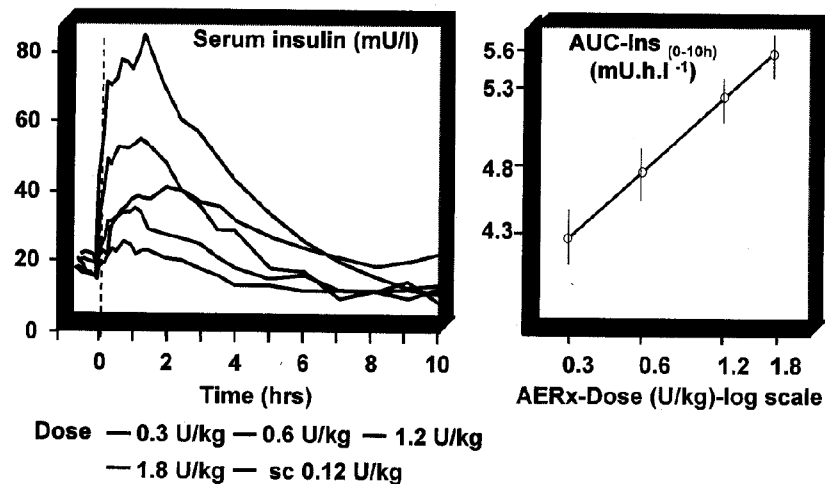


Figure 4. Mean serum insulin profiles over ten hours after inhaled insulin (liquid aerosol formulation), administration, using the AERx® insulin delivery system (Aradigm Corp. and Novo Nordisk A/S) at different doses at 0 min, together with the estimated dose–response relationship (with 95% confidence interval). Adapted from Brunner *et al.*⁸⁵.

post-administration period, was 23, 16 and 10% respectively⁹³. The within-subject variability in peak insulin concentration, the time to maximum insulin concentration and the glucose infusion rate with the inhaled insulin, given on three days during an euglycemic clamp study in patients with Type 2 diabetes, were 27, 23 and 20% respectively⁹⁴. These values are similar to those seen previously in healthy subjects with subcutaneous soluble insulin.

Ease of use and patient acceptance will greatly influence the choice of delivery system, especially when considering the requirements of groups such as children and the elderly. For patients with airflow obstruction, intrapulmonary delivery of insulin is less appropriate. It is also known that up to two-thirds of long-standing diabetic patients has some abnormality of lung function⁹⁵. Special caution also needs to be exercised when intrapulmonary insulin is given to patients who are smokers due to the very rapid absorption. Similarly, exercise may enhance the pulmonary absorption of inhaled insulin.

Clinical experience to date with inhaled insulin has revealed little in the way of local adverse reactions other than increased coughing and throat clearing associated with the act of inhalation in approximately 10% of

patients⁸². Limited lung function tests have also remained essentially unchanged in patients treated for up to one or two years although there is a consistent non-significant trend to a reduction across the spectrum of pulmonary function tests (spirometry, lung volume and diffusion capacity) compared to subcutaneous insulin control groups. The frequency and severity of hypoglycemia is equivalent to that experienced with subcutaneous administration⁸².

In clinical terms, the onset of action of inhaled insulin is comparable to the rapid-acting insulin analogues but with a slightly more prolonged effect making it suitable for meal-related insulin supplementation. There is concern about the potential effect of supraphysiological concentrations of insulin on the pulmonary vascular bed, leading to pulmonary hypotension and pulmonary oedema especially in patients with cardiac dysfunction⁹⁶. Insulin's proinflammatory effects may also accentuate airway obstruction⁹⁷. Its essential use will depend on long-term efficacy and safety, quality of life^{83,84,98} and cost–benefit analysis. Patient education needs to be an essential part of the introduction of any inhaled insulin into clinical practice. Translating differences between delivery devices into clinical benefits will require extensive clinical experience, necessary also in designing future delivery systems.

Summary

Ever since subcutaneous insulin therapy was introduced, attempts have been made to explore alternative, less invasive routes of delivery. There appears little or no justification in pursuing the nasal, dermal, ocular, vaginal or rectal routes due to persistently low and variable bioavailability. The ultimate ambition to deliver insulin via the oral (gastrointestinal) route continues to face a multitude of obstacles, making it an unrealistic endeavour. Renewed attempts at enhancing the buccal absorption of insulin are underway.

Interest in the intrapulmonary route has recently been regenerated, with the development of new delivery devices for dry powder or liquid aerosol formulations. Improving the delivery of insulin into the deep lung (alveolar surface) has benefited from a better understanding of the impact of aerosol particle size, inspiratory flow rate and inhaled volume. The delivery system efficiency will depend not only on maximising the output of fine particles, but also on optimizing the inspiratory flow rate and inhaled volume, to achieve a consistent and acceptable level of bioavailability. Inhaled insulin is quickly absorbed and the bioavailability rarely exceeds 20%. Whereas little or no metabolic advantage from inhaled insulin can be expected when compared to the rapid-acting insulin analogues, the avoidance of pre-meal subcutaneous injections remains a major incentive given the current advocacy for intensive insulin therapy. Complete avoidance of subcutaneous injections still cannot be achieved in patients with Type 1 diabetes due to the need for supplementary basal insulin.

In the wake of the DCCT study, there has been a resurgence of interest in external (CSII) and implantable pump devices. Inextricably linked is the evolution of glucose sensors to allow optimization of therapeutic strategies. The eventual goal is to develop miniature external or implantable 'closed-loop' systems (artificial pancreas) with the infusion of insulin controlled automatically to maintain the blood glucose within pre-defined limits. However, the recent availability of a new long-acting insulin analogue (insulin glargine) used along with the rapid-acting analogues provides a real alternative. Other options include islet cell transplantation⁹⁹ and on the horizon advancements in cell biology and genetics¹⁰⁰ may provide the final opportunity for insulin independence.

In the meantime, the subcutaneous route of insulin delivery will remain dominant. However, recent clinical studies with inhaled insulin suggest a possible role in patients with Type 1 and Type 2 diabetes. One major contribution would be facilitating the earlier introduction of insulin in patients otherwise inadequately controlled with Type 2 diabetes. Many patients will welcome reducing the number of injections through inhalation. The influence of smoking, obstructive and interstitial lung disease and possibly exercise, on the absorption of

inhaled insulin needs to be taken into consideration in the clinical setting. Both the acute and especially long-term safety of inhaled insulin requires continued surveillance with the fate of inhaled insulin still to be elucidated. Agreement on methods to determine safety of inhaled insulin remains a priority along with standardizing methods for estimating bioavailability to allow meaningful comparison between the different delivery devices and/or insulin formulations.

A plea is also made to manufacturers to better define the functionalities of their delivery devices where precision of dosing, dose increments and reproducibility will remain key elements in the validity of this approach.

There is a distinct possibility that the intrapulmonary delivery of insulin will become the first widespread non-subcutaneous route of administration. This new millennium promises a major change in the delivery of insulin, which cannot come too soon for the billions reliant on subcutaneous administration. Cautious optimism based on scientific rigour is the only way forward.

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