Inhaled insulin: A model for pulmonary systemic absorption?

L’insuline par voie inhalée : un modèle pour l’absorption systémique pulmonaire ?

M.-H. Becquemin\textsuperscript{a,*}, J.-P. Chaumuzeau\textsuperscript{b}

\textsuperscript{a} UPRES 2397, faculté de médecine, université Denis-Diderot, Paris VII, groupe hospitalier Pitié-Salpêtrière, 75013 Paris, France
\textsuperscript{b} Groupe aérosol thérapie, société de pneumologie de langue française, 75006 Paris, France

Available online 23 May 2010

Summary  The European Union recently approved a form of insulin intended to be inhaled. This innovative presentation has the potential to partially or completely replace the injections and thus facilitate starting insulin therapy which is considered with apprehension and often differed. On this occasion, we reviewed the issues raised by this pulmonary route for systemic absorption (anatomical and cytological limits, cellular mechanisms, relevant physical parameters, facilitating chemical cofactors, role of tobacco smoking and of common respiratory diseases). The pharmacokinetics of inhaled and injectable insulins are comparable, apart from an appreciably faster absorption of the former, and both show the same intra-individual variability. The total bioavailability is definitely lower with the inhaled route but is notably increased in smokers. These characteristics can vary according to the inhalation system used. A frequent induced cough, the increase in circulating anti-insulin antibodies, and a potentially higher cost are not really determining obstacles. The indications will have to be clearly specified and the long-term innocuousness of repeated inhalation of such a mitogen, especially in children and former smokers, remains to be fully proven.

© 2010 SPLF. Published by Elsevier Masson SAS. All rights reserved.


Corresponding author. Service central d’explorations fonctionnelles respiratoires, groupe hospitalier Pitié-Salpêtrière, 75651 Paris cedex 13, France.
\textit{E-mail address:} marie-helene.becquemin@psl.aphp.fr (M.-H. Becquemin).

0761-8425/\$ -- see front matter © 2010 SPLF. Published by Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.rmr.2010.04.004
The recent marketing in the United States, and soon in France, of a form of insulin intended to be inhaled is news of interest to chest physicians for several reasons:

- purely from the design point of view, this administration route goes against their usual approach directed at giving preference to local topical action while minimizing systemic effects;
- this different treatment form, at least in the case of prolonged use, will require their intervention for the surveillance of possible adverse effects and screening for contraindications;
- their opinions as specialists could also be requested by diabetologists and endocrinologists with little experience of such a specific administration route.

We thus take this opportunity to examine the advantages and disadvantages of this administration route, and more generally, the problems raised by pulmonary systemic absorption, its limits and possible solutions.

Background

The preliminary communication by F. Banting and C. Best on an aqueous pancreatic extract with powerful antidiabetic activity was in December 1921 [1], at the time when the first injection was administered to a diabetic patient on 11 January 1922 [2].

From 1924, two teams working independently, Von Heubner in Amsterdam and Muller in Tubingen (Germany), demonstrated the hypoglycaemic action of inhaled liquid insulin, resulting in the first two publications on the subject [3,4]. There were no practical applications because of the bulky devices used at that time, the low aerosol output produced, and the time constraints. A 46-year wait was required until 1971 when Wigley et al. [5] demonstrated that nebulisation of porcine insulin increased plasma concentrations of insulin, and that these showed correlation with the hypoglycaemic action obtained. The first general critical review of the use of inhaled insulin in humans was in 1978 [6]. In 1987, two complementary studies were performed in both adults and children confirming that inhalation was a possible and effective administration route for insulin [7,8].

With identification of the main pulmonary absorption parameters [9] (appropriate particle size, appropriate ventilation characteristics, deposition deep in the lungs), industrial development proceeded in 1996–97. Several pharmaceutical companies, mainly American, then started their research programmes. In 2000, the first patents were registered in the United States. In January 2006, the first inhaled powder form of recombinant human insulin was granted European Union marketing authorization and FDA validation [10], while development of insulins with a long duration of action for inhalation (with the addition of polyethylene glycol or protamine zinc insulin-based) had hardly passed the preliminary study stage [11,12].

The rational behind the issue

Why an inhaled form of insulin?

Like many peptides, insulin (composed of 51 amino acids) is not absorbed in the digestive tract because of local enzyme activity and the absence of an appropriate transcellular transport path.

Injection, intramuscular, intradermal and mainly subcutaneous, became established very early as the most suitable route because it was generally well accepted. However, apart from its sometimes disagreeable nature, this administration route has several drawbacks, in particular its imperfect reproducibility, the risk of lipodystrophy and even insulin resistance, the heat sensitivity of solutions that must be kept cool, and the low concentration/volume ratio.

The main barriers nevertheless remain psychological (fear of injections, [13] insurmountable anxiety concerning self-injection, the impression of worsening caused by the use of insulin considered to be the last recourse), and explain the often considerable delay in implementing this treatment [14].

Practically all the alternative routes have been tested [15–17]: transdermal, intranasal, oral, pulmonary, even conjunctival and rectal, nearly always with disappointing results [18].

Only the peritoneal route (portable pump with an implanted catheter) has to date proven its good acceptability and efficacy. However, the technique remains little used, particularly in France. To date, the treatment regimen for practically all type 1 diabetics is three or four subcutaneous injections a day (with in addition self-monitoring of finger-prick blood glucose levels). The total number of needle pricks can reach 12 to 15 a day (insulin injections and pinprick tests), particularly in the context of flexible insulin therapy, and whatever the scenario, largely exceeds 15,000 needle pricks in 10 years!

Under these conditions, the interest in a potentially non-aggressive and painless inhaled administration route, without major drawbacks, is understandable.

- The parenteral route has several drawbacks: imperfect reproducibility, risk of lipodystrophy and even insulin resistance, heat-sensitivity of the solutions, low concentration/volume ratio, and mainly the psychological rejection.
- Currently, practically all type 1 diabetics are treated with three or four subcutaneous injections a day.

Pulmonary systemic drug absorption: what are the limits? What are the constraints?

From the anatomical and morphological viewpoints

The alveolocapillary membrane is an ideal site for exchanges between the exterior environment and the blood compartment [19,20]:
- large surface area (100 to 120 m² on the alveolar side, 70 to 80 m² on the capillary side);
- the parenteral route has several drawbacks: imperfect reproducibility, risk of lipodystrophy and even insulin resistance, heat-sensitivity of the solutions, low concentration/volume ratio, and mainly the psychological rejection.
- Currently, practically all type 1 diabetics are treated with three or four subcutaneous injections a day.

• The parenteral route has several drawbacks: imperfect reproducibility, risk of lipodystrophy and even insulin resistance, heat-sensitivity of the solutions, low concentration/volume ratio, and mainly the psychological rejection.
• Currently, practically all type 1 diabetics are treated with three or four subcutaneous injections a day.

From the anatomical and morphological viewpoints

The alveolocapillary membrane is an ideal site for exchanges between the exterior environment and the blood compartment [19,20]:
- large surface area (100 to 120 m² on the alveolar side, 70 to 80 m² on the capillary side);
• very thin (< 2 μm);
• abundant ventilation on one side (6 to 7 L/min), abundant vascularisation on the other (approximately 5 L/min);
• low enzyme component (in particular few peptidases) [21,22] with practically no mucociliary clearance [23];
• easy to use, simple and physiological.

From the ultrastructural point of view

The various layers to be crossed are successively [24]:
• surfactant: a monomolecular phospholipid layer with surface active properties that tend to block dissolution of solid particles because of its aggregation capacity;
• fluid layer: immediately underneath whose composition (rich in potassium, poor in proteins) is very different to bronchial mucus, but whose role in the fate of inhaled molecules is only just becoming known;
• alveolar epithelium: composed of a single layer of large and thin type 1 cells, and small and compact type 2 cells; approximately a hundred cells line each alveolus. This alveolar epithelium constitutes 90% of the barrier to alveolar transport [25];
• basal membrane: composed of a thin fibrous extracellular matrix in the interstitial layer, it acts as a rigid filter but does not seem to be a significant barrier to the transport and absorption of molecules;
• vascular endothelium: composed of a single layer of cells at the origin of the pulmonary capillaries. This structure is considered to be far more permeable to proteins than alveolar epithelium.

The total thickness of these superimposed layers does not exceed 2 μm.

The absorption mechanisms

The details are still not well known, but there are probably two types [24]:
• transcytosis: corresponding to the transport of molecules by intravesical inclusion through the epithelial then endothelial cells by an endocytosis-exocytosis mechanism, with or without the intervention of a receptor in the membrane. This is probably the main absorption mechanism for inhaled insulin;
• paracellular transport: takes place in the interstices at the junction of two or three contiguous cells, or through the large pores transiently resulting from the deterioration or death of an epithelial cell.

Additional factors

Multiple additional factors play an important role in optimal intra-alveolar deposition and pulmonary absorption [26], mainly:
• the size of the particles (between 1 and 3 μm in aerodynamic diameter) and their low velocity (slow and deep inspiration with an inspiratory flow < 30 L/min) [27,28], particularly with high lung volumes at maximum inspiration [29];
• the size and molecular weight of the medicinal substance. Pulmonary absorption is inversely proportional to molecular weight, with a maximum limit of approximately 40 kDa and 5 to 6 nm, i.e. a value far superior to that of insulin which is a small molecule (5.7 kDa and 2.2 nm);
• the physiochemical characteristics, particularly lipophilic and hygroscopic that facilitate absorption, and a negative electric charge;
• smoking that considerably increases the permeability of alveolocapillary membrane to proteins and medicinal substances such as insulin [30–32]. This modification in permeability is related to deterioration and desquamation of type 1 epithelial cells affecting above all the bronchioloalveolar junction zones; it is more or less reversible after cessation of smoking [33] and is important enough to significantly modify the bioavailability of inhaled insulin that can be multiplied by three in active smokers;
• acute, and mainly chronic, intercurrent bronchopulmonary disorders result in inflammatory deterioration of the distal airways and disturbance of alveolar ventilation that modifies the quality and reproducibility of pulmonary absorption. This is particularly the case in asthma that reduces insulin absorption [34] and in COPD;
• some enhancer agents are also likely to considerably increase pulmonary absorption of peptides and proteins [35,36]. These include surfactant, bile salts, fatty acids and chelating agents. Unfortunately, these substances have their own toxicity, particularly long-term as their mechanism of action is through tissue irritation or disturbance in the architectural arrangement of cells [37].

The development of new dosage forms using vectors such as liposomes or polymer nanospheres should enable considerable improvement in pulmonary resorption of peptides and proteins [38] for therapeutic use.

Apart from licit (smoking) or illicit (ether, hashish) non-medical use, the administration of medicinal substances by pulmonary route for systemic effect is still very limited, whether in the form of gases (volatile anaesthetics), specific aerosols (insulin), or by nebulisation (iloprost, fentanyl, apomorphine). The use of other medications such a heparin or some vaccines has never advanced beyond the experimental stage.

The theoretical limits of the inhaled route for systemic absorption

These are numerous:
• the applicable threshold of tolerance for inhalation of non-soluble particles is fixed at 30 mg/day. There is also a theoretical threshold for the possible use of a medication by pulmonary route; this results from the relationship between the minimum indispensable effective dose that must be resorbed and distributed in the body to obtain a significant pharmacological action on the one hand, and the dose that can be administered by inhaled route considering the volume of aerosolised solution, the required administration time, and the maximum percentage absorbed on the other hand [39];
• this simple calculation shows that in theory we could consider the administration of medications by inhalation such as corticosteroids, hormones, and some analgesics, while antibiotics, systemic chemotherapy and NSAIDS for example cannot in principle be administered using this route. Obviously, there is a pharmacological limit to the preparation of a nebulised form in terms of real administrable dose/minimum effective dose ratio;
Inhaled insulin: A model for pulmonary systemic absorption?

- In general, powdered forms present advantages over liquid solutions for nebulisation (stability at room temperature, low risk of microbial proliferation, higher unit concentration) [40].

- Pulmonary absorption is through two routes: transcytosis and paracellular transport.
- Absorption involves several factors: particle size and velocity, active ingredient molecule size and weight, physiochemical characteristics of the substance (lipophilic, hygroscopic, electric charge), smoking and possible bronchopulmonary disorders (asthma and COPD), presence of surfactant, bile salts, fatty acids and chelating agents.
- The inhaled route has limits: the tolerance threshold applicable to inhalation of insoluble particles, and pharmacological limits of the nebulised form (real administrable dose/minimum effective dose ratio).
- Powdered forms present advantages over liquid solutions.

### Pharmacokinetics and pharmacodynamics of inhaled insulin

Pharmacological studies conducted using the various inhalation systems available [41—44] show some concordant characteristics.

Even though comparisons are difficult considering the different forms, concentrations and technologies used by the inhalation systems, insulin is generally absorbed more rapidly, or at the least as quickly, by inhaled route than by subcutaneous route with a time to maximum serum concentration (Tmax) of 7 to 80 min (against 42 to 274 min by injectable route). This absorption is biphasic with a rapid spike followed by a second slower phase.

Bioavailability is markedly higher in smokers with a peak insulin concentration (Cmax) that can be tripled even though the blood concentration spike does not occur earlier [45]. Smoking cessation does not result in complete normalisation of values, even after an initial interval of three months.

The glucodynamic profile showed that the hypoglycaemic effect is more rapid with inhaled insulin and the maximal metabolic effect is at least equal to that of injectable insulin. The dose—response relationship is roughly linear [46,47]. Inhaled insulin is longer-acting than insulin lispro, approximately 6 hours, but equivalent to that of human insulin by subcutaneous route. In general, there are less episodes of hypoglycaemia [48,49]. The total bioavailability of inhaled insulin is low as 50 to 80% of the inhaled dose does not reach the deep lung and is lost due to deposition in the device and in the upper or intrapulmonary airways, or is exhaled. Depending on the system, the values measured are between 9 and 22%, which means that to obtain the same effect five to 10 times more insulin must be administered than by subcutaneous route. For example, 1 mg of Exubera corresponds to 27.5 units of human insulin with the same bioefficacy as three units of subcutaneous insulin lispro [50]. Its bioavailability is relatively satisfactory as approximately 40% of the dose actually deposited in the alveoli is rapidly absorbed in the systemic circulation.

Pharmacokinetic intra-individual variability is 15 to 30%, i.e. identical to the values calculated with subcutaneous administration [32] in both healthy volunteers and diabetic patients. It is however far higher in asthmatic subjects [34].

In elderly patients, there are no real differences in the pharmacokinetics of inhaled insulin [51], but insulin resistance tends to increase with ageing.

- Inhaled insulin is absorbed more rapidly, or at least as quickly as subcutaneous insulin.
- The hypoglycaemic effect is more rapid with inhaled insulin and the maximal metabolic effect is at least equal to that of injectable insulin.
- Its duration of action is approximately 6 hours.
- There are less episodes of hypoglycaemia with inhaled insulin.
- The bioavailability of inhaled insulin is low, between 9 and 22% depending on the system.
- Pharmacokinetic intra-individual variability is between 15 and 30%, identical to the values with subcutaneous insulin.
- Insulin resistance increases with ageing.

### Systems in development

A recent meta-analysis by Ceglia et al. [52] collected the results of 16 phase III open-label studies with a minimum duration of 12 weeks (from 1966 to June 2006) involving a total of 4023 patients (18—80 years) with type 1 and 2 diabetes. The analysis compared both administration methods, inhaled versus subcutaneous (randomised trials). It showed a slightly greater reduction in glycated haemoglobin (HbA1c) levels with subcutaneous insulin, but this difference remained very low at 0.08% (0.03—0.14) in absolute terms. However, concerning the reduction in HbA1c level of ≤ 7%, there was no significant difference between the percentage of patients treated by inhaled versus subcutaneous route. Moreover, the inhaled route showed a greater reduction in HbA1c of −1.45% (−1.80 to −1.10%) in absolute terms than oral hypoglycaemic agents prescribed at fixed doses, but far less than when oral hypoglycaemic agent doses were adjusted to blood glucose levels, with a reduction in HbA1c levels of −0.20% (−0.34 to −0.07%). Episodes of severe hypoglycaemia were more frequent with inhaled insulin versus oral hypoglycaemic agents but identical to those with subcutaneous insulin.

There have been many publications on devices currently under study for aerosol delivery of insulin [2,16,53,54] resulting from active pharmaceutical industry research in development of new technologies. These systems must, at the same time, produce particles with the appropriate size, provide optimal inhalation, and deliver in a reproducible manner the medicinal substance intact to the alveoli to avoid episodes of hypo- or hyperglycaemia [41,55,56].

The formulation used is:
either insulin in dry power form:
- Exubera Device,
- Technosphere™ Insulin,
- Spiros Device,
- or insulin adsorbed on porous particles: Air™ Pulmonary Drug System Device;

or insulin in nebulised liquid form:
- AERx® (iiIDMS),
- Aerodose™ inhaler,
- Kos Device.

Devices using dry powder insulin

Exubera Device (Nektar Therapeutics Inc., San Carlos, CA, Aventis, Bridgewater, NJ, Pfizer, NY, USA) (Fig. 1)

Exubera is the only system currently marketed. It is a dry powder containing recombinant human insulin [57] presented in blisters to be inserted in an inhaler. As for all powder forms, there are problems with hygroscopicity [58] and intra- and interindividual variability related to the inhalation technique [59]. However, the mannitol is used as an excipient and the design of the inhalator minimises their impact. It does not use gas for propulsion or require electrical energy. The blister is placed in a slot situated between the upper and lower chambers. The patient presses on a button that pierces the blister and an air compression mechanism [60] disaggregates the powder which disperses in the transparent upper chamber similar to an inhalation chamber (volume below 20% of inspiratory reserve volume). The patient can thus see the aerosol whose mass median aerodynamic diameter (MMAD) is close to 3 μm, then turns the mouthpiece and takes a long and deep inspiration, either standing or sitting. The entire device fits in a 16 cm cylinder and can be cleaned twice a week.

Each blister or thermoformed tray containing a 1 or 3 mg dose, equivalent to 3 or 8 IU of injectable rapid-acting insulin, can be stored at room temperature.

The efficacy of Exubera has been demonstrated in 2500 adults, with a more rapid insulin spike at 49 min (60—90 min) compared with that of conventional insulin administered subcutaneously at 105 min (60—240 min).

In type 2 diabetes, it can be used alone or in association with an oral hypoglycaemic agent or with a long-acting insulin. Exubera should not be prescribed for smokers or former smokers who stopped less than 6 months previously, or for subjects with asthma, COPD, or emphysema.

In type 1 diabetes, the control of blood glucose levels is identical (series of 47 to 335 patients for a duration of 3 to 6 months) when comparing preprandial inhaled insulin (PPII) associated with ultralente insulin [48,61] or with NPH insulin [62,63] versus injections of NPH insulin associated with conventional insulin.

In type 2 diabetes, several open-label randomised studies (series of 26 to 309 patients for a duration of 3 to 6 months), comparing PPII alone [64] or associated with an oral hypoglycaemic agent [65], versus an oral hypoglycaemic, or PPII with ultralente insulin and dose adjustment each week [50], have shown a significant reduction in HbA1c and improved control of blood glucose levels with PPII. Identical control was observed in a study of 145 patients (not controlled with diet before treatment) with PPII alone versus oral hypoglycaemic treatment [66], and in another study of 299 patients [49] with PPII associated with ultralente insulin versus at least two injections of mixed insulin. However, studies have shown that PPII provided a quite significant increase in acceptability and better compliance with insulin therapy for these patients [67], and that they preferred inhaled to subcutaneous administration [68].

Technosphere™ Insulin (Pharmaceutical Discovery Corporation MannKind Biopharmaceuticals, NY, USA) (Fig. 2)

This is insulin formulated as a crystalline powder with an aerodynamic diameter of 3 μm, in capsules presented in three strengths corresponding to the equivalent of 2, 4 and 8 IU of injectable insulin. The aerosol, composed of insulin particles loaded onto diketopiperazine molecules, is produced using an inhaler triggered when the patient inhales [69]. The device is small and easily carried. Studies of healthy subjects and type 2 diabetics have shown an intermediate action-time profile, between IV and SC insulin. The insulin spike is rapid at 13 min [55], onset of action is between 20 and 30 min, and duration of action is brief at 2 to 3 hours. Intra-individual variability remains low [70,71].

Spiros™ Device (Dura Pharmaceutical) (Fig. 3)

Currently under development, this inhaler (Spiros-S2) delivers an aerosol of powdered insulin for low inspiratory flow rates of 15 to 30 L/min. An open-label randomised study with this device [72,73] of 13 non-smoker healthy volunteers, comparing four doses of inhaled insulin (60, 90, 120 and 150 U) with three doses of subcutaneous insulin (8, 14 and 20 U), showed better efficacy for the inhaled form in terms of pharmacokinetics and bioavailability.
Inhaled insulin: A model for pulmonary systemic absorption?

Figure 2. Technosphere™ insulin.

Air™ Pulmonary drug system device (Advanced Inhalation Research, Alkermes, MA, and Eli Lilly, Indianapolis, USA) (Fig. 4)

The Air system uses porous particles with a geometric diameter between 5 and 30 μm. As the particles are very low in density (< 0.03 g/cm³), their aerodynamic diameter, proportional to the square root of their density, is small at 1 to 5 μm. The porous nature of the particles, by minimising the tendency to particle aggregation, facilitates their dispersion and enables better absorption [74,75]. The data obtained in the rat showed comparable pharmacokinetics with inhaled insulin using this device and fast- and slow-acting insulin [12]. A 12-week study of 259 patients with type 1 diabetes randomised to two groups (inhaled insulin versus subcutaneous insulin) showed comparable efficacy in terms of HbA1c level, episodes of hypoglycaemia, and CO diffusion in both groups [76]. Another study [77] showed that insulin delivered with this system had a comparable onset time to insulin lispro but a significantly longer duration time (480 min) than insulin lispro (360 min) and human insulin (415 min).

Devices using insulin in nebulised liquid form

AERx® (Insulin Diabetes Management System [IDMS]) (Aradigm Corporation, Hayward, CA, USA and Novo Nordisk A/S, Copenhagen, Denmark) (Fig. 5)

This system uses a principle similar to sieve-type devices delivering nebulised insulin with an MMAD between 1 and 3 μm [55,78]. A microprocessor automatically triggers the aerosol only when predefined inspiratory conditions (inspired volume, inspiratory flow) coincide [79]. Once the aerosol is generated, the system uses a breath-guidance system to enable the patient to obtain optimal inspiratory flow and volume. Then, at the end of inspiration, 400 ml of air is delivered to carry the aerosol to the peripheral lung.

The insulin is stocked in unit dose form, and the system can deliver 1 to 10 units in 1-unit increments. Scintigraphy studies have shown reduced inhaled dose variability with this system [79–81]. Moreover, the device memorises the dose, date and ventilatory parameters for each inhalation, which facilitate patient compliance and treatment surveillance [82].

Deposition in the deep lung is generally between 10 and 20% with conventional devices, whereas with this system it can reach 50% [80], with a far more rapid onset of action (7–20 min) compared with SC insulin (100–120 min) [79].

A study of 18 patients with type 1 diabetes [46] confirmed more rapid absorption and metabolic effect with a shorter onset of action than with SC insulin. Another study
of 107 patients with type 2 diabetes for 12 weeks showed that preprandial administration of inhaled insulin with the AERx® system showed identical results in terms of HbA1c compared with those for SC insulin [83,84]. Upper respiratory tract infection did not seem to modify pharmacokinetics [85]; this was not the case with asthmatic patients [34,86].

With the AERx® system, intra-individual variability of absorption appeared to be less (approximately 20%), in both non-smokers and smokers, compared with SC insulin [87].

AerodoseTM Inhaler (Aerogen Inc., Sunnyvale, CA, USA) (Fig. 6)

This battery-operated electronic generator delivers, for an inspiratory flow superior to 15 L/min, nebulised fluid insulin with an MMAD of 3.3 μm and a respirable fraction of 87% [88]. A study of 13 healthy volunteers showed that, with this system, it was more the aerosolisation time than particle size that had a real impact on the metabolic effect of the insulin [89]. Again, in healthy subjects, time to peak insulin level is more rapid (50 min) with the inhaled versus the subcutaneous form (85 min) and bioavailability is 9.3%. Likewise, this peak was earlier with inhaled insulin in a study of subjects with type 2 diabetes [90—92].

Kos inhaled insulin (Kos Pharmaceuticals, Cranbury, NJ, USA) (Fig. 7)

This nebulisation device currently under development incorporates an electric counter for better monitoring of the doses delivered. A canister contains liquid insulin for the delivery of up to 120 doses. A study of 20 healthy subjects [77] comparing inhaled insulin and rapid-acting subcutaneous insulin showed an identical insulin spike (45 min) for both administration forms, but a longer duration of action for the inhaled form (412 against 236 min), better adapted to the treatment of late onset postprandial hyperglycaemia. In another study [93], inhaled insulin using this device 15 min before meals versus subcutaneous insulin at bedtime provided better control of blood glucose levels in 24 patients with type 2 diabetes previously poorly controlled with oral hypoglycaemic agents.

- The reduction in glycated haemoglobin (HbA1c) level is identical with both administration routes (inhaled and subcutaneous).
- The inhaled route provides a greater reduction in HbA1c level than fixed-dose oral hypoglycaemic agents, but far less than oral hypoglycaemic agents at doses adapted to blood glucose levels.
- Inhalation systems must generate particles of appropriate size, provide optimal inhalation, and deliver the medicinal substance intact to the alveoli, in a reproducible manner.
- The insulin is presented in either dry powder or liquid form.
- There are many administration devices, for insulin in either dry powder or nebulised liquid form.

The drawbacks and potential reservations

Insulin is a peptide with anabolic properties

Insulin is a peptide with anabolic, proinflammatory and immunoreactive properties that contribute to the multiplication of alveolar epithelial cells, block apoptosis, and cause capillary vasodilation.

Inhaled insulin is, by definition, likely to be administered for extremely long periods.

These elementary observations encourage prudence concerning long-term tolerance, as the interpretation of pulmonary function tests is complicated.
Diabetes itself causes pulmonary impairment [94]. Little-known and underdiagnosed, this microangiopathy involves the alveolar septal capillaries and the pleural arterioles, and has similarities with renal, retinal, neurological and myocardial microvascular disorders [95,96].

The pulmonary lesions observed associate thickening of the basal lamina, intraseptal nodular fibrosis and emphysema-like features.

The pulmonary function abnormalities frequently observed in non-smoking patients with poorly controlled type 1 diabetes [97,98] are a reduction in volume of 8 to 20%, and a marked diminution in pulmonary CO diffusion capacity that can reach 35% without associated obstructive disorders. At least partial reversibility of these abnormalities is possible with intensive treatment of diabetes and the return to good control of blood glucose levels.

What are the potential effects of the medication on pulmonary tissue?

What interference is there between the adverse effects of inhaled insulin and the complications of diabetes itself? (The surveillance criteria, FEV1 and DLCO, being identical). What local role can a powerful mitogen play, particularly in former smokers?

Some aspects are reassuring:
- no significant abnormalities of pulmonary function have been recorded after follow-up for 4 years [99].
- a little over 10% of the inhaled dose is delivered to the alveoli; each dose delivered distributes approximately one particle of insulin by alveolus, i.e. approximately 1% of the alveolar cells are impacted at each administration.

The definitive global tolerance results will however not be known or available before 2014–2016. Until then, prudence is necessary.

Insulin has immunogenic properties

Insulin also has immunogenic properties that result in the formation of circulating insulin antibodies [100]. This antigenic response is markedly superior in subjects administered inhaled insulin compared with subcutaneous insulin. It affects more particularly patients with type 1 diabetes. It is a relatively early IgG type reaction with peak serum antibody levels recorded between the 6th and 12th months of treatment. The potential risks (partial blockage of activity, neutralising power, precipitation later) seem to be more theoretical than real as no interference has been reported to date in terms of control of blood glucose levels, frequency of hypoglycaemic episodes, variations in dosage, or modifications in pulmonary function.

General drawbacks of inhaled insulin

The general drawbacks of inhaled insulin should not be overlooked:
- cough is the most frequently reported symptom [101] in around 25% of cases. It occurs in the first weeks of treatment and tends to diminish with time. It only exceptionally results in the interruption of the treatment;
- the possible chronic toxicity of the absorption enhancers and excipients (in particular mannitol, glycine, citrate and sodium hydroxide) is not really known;
- the quite small therapeutic index requires obtention of good reproducibility of pulmonary deposition and the quantity absorbed [54];
- the low bioavailability of the product by inhaled route and its direct corollary, the need to administer high doses, results in a theoretical risk of passive inhalation of the exhaled part for people in close proximity, and above all an appreciable additional cost due to the quantity of medication lost, on top of the cost of the inhalation system [102];
- this administration route is contraindicated in smokers [103] and asthmatic patients and presents an appreciable practical problem, even though overall patient satisfaction and compliance with treatment seem to be indisputable [104–106].

Finally, the fundamental issue is the real interest of this dosage form. Inhaled insulin is in no way a substitute for a supplementary daily or twice-daily injection of ultralente insulin, nor does it have any influence on the need for self-monitoring of blood glucose levels with finger-prick tests several times a day; these are far more disagreeable and painful that injecting insulin in the not very sensitive skin of the abdomen or thighs.

These unanswered issues certainly contributed to the strong reservations expressed in the opinion of the British National Institute for Health and Clinical Excellence [107,108] that, for the time being, does not advise the systematic use of inhaled insulin and advises against validation of its availability in the NHS until a new reassessment.

- Insulin has anabolic, proinflammatory and immunoreactive properties that contribute to the multiplication of alveolar epithelial cells, block apoptosis, and cause capillary vasodilation; this encourages prudence concerning long-term tolerance.
- Diabetes causes microangiopathy involving the alveolar septal capillaries and the pleural arterioles.
- The frequent pulmonary function abnormalities in non-smoking patients with poorly controlled type 1 diabetes are a reduction in volume of 8 to 20%, and a marked diminution in pulmonary CO diffusion capacity that can reach 35% without associated obstructive disorders.
- Tolerance is not yet well known and will not be before 2014–2016; until then prudence is necessary.
- Inhaled insulin has several drawbacks: cough, potential toxicity of excipients, small therapeutic index, low bioavailability, contraindication of its use in smokers and asthmatic patients.

Conclusion

Inhaled insulin, whose profile of action is comparable to rapid-acting subcutaneous insulin, could be proposed for preprandial administration in both types of diabetes [109], in replacement of or in addition to oral hypoglycaemic
agents or injections of insulin, to improve control of blood glucose levels.

To date, it is an interesting and innovative dosage form for its design, easy administration, and efficacy, but potentially expensive compared with the conventional injectable form.

The indications for inhaled insulin require refining, and its long-term innocuousness requires formal proof, particularly in children and former smokers.

**Addendum**

The marketing project for Exubera in 2008 was cancelled in Europe for business reasons.

**KEY POINTS**

- The inhaled route could be an alternative to intramuscular, intradermal and mainly subcutaneous injections.
- Only the peritoneal route has to date proven its good acceptability and efficacy.
- The alveolocapillary membrane is an ideal site for exchanges between the exterior environment and the blood compartment.
- Pulmonary absorption is through transcytosis and paracellular transport.
- Several factors are involved in alveolar deposition and pulmonary absorption, such as particle size, physiochemical characteristics of the substance, and associated bronchopulmonary disorders.
- The development of new dosage forms using vectors such as liposomes or polymer nanospheres should enable considerable improvement in pulmonary resorption.
- There are many administration devices, for insulin in either dry powder or nebulised liquid form.
- The effects of long-term inhaled administration have not yet been ascertained.

**Conflict of interest statement**

None.

**References**


Inhaled insulin: A model for pulmonary systemic absorption?


[90] Perera AD, Kapitza C, Nosek L, Heinemann L, Shapiro DA, Fishman TC, et al. Reproducibility of inhaled and subcu-


[96] Popov D, Simionescu M. Alterations of lung structure in experimental diabetes, and diabetes associated with hyper-


Inhaled insulin: A model for pulmonary systemic absorption?


