Alternatives routes of insulin delivery

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SUMMARY
Optimal glycaemic control is necessary to prevent diabetes-related complications. An intensive treatment, which could mimic physiological insulin secretion, would be the best one. However subcutaneous insulin treatment is not physiologic and represents a heavy burden for patients with type 1 and type 2 diabetes mellitus. Consequently, more acceptable, at least as effective, alternative routes of insulin delivery have been developed over the past years. Up to now, only pulmonary administration of insulin (inhaled insulin) has become a feasible alternative to cover mealtime insulin requirements and one of the various administration systems was recently approved for clinical use in Europe and the United States. But, due to advances in technology, other routes, such as transdermal or oral (buccal and intestinal) insulin administration, could become feasible in a near future, and they could be combined together to offer non-invasive, efficacious and more physiological way of insulin administration to patients with diabetes.

Key-words: Routes of insulin delivery • Ocular, Oral, Buccal, Intestinal, Nasal, Pulmonary, Inhaled insulin • Review.

RéSUMÉ
Voies alternatives d’administration de l’insuline
Un contrôle glycémique optimal est indispensable pour prévenir les complications du diabète. Un traitement intensifié, reproduisant la sécrétion physiologique d’insuline, représenterait l’idéal. Mais le traitement par insuline par voie sous-cutanée n’est pas physiologique et les schémas basal-bolus représentent un lourd fardeau pour les patients atteints de diabète de type 1 et de type 2. Aussi, depuis longtemps, ont été recherchées des voies alternatives d’administration de l’insuline, plus physiologiques, plus acceptables, et au moins aussi efficaces. Jusqu’à ce jour, seule la voie pulmonaire (insuline inhalée) représente une alternative pour les besoins en insuline prandiaux, et l’un des systèmes d’inhalation d’insuline a été approuvé en 2006 par les autorités de santé européennes et par celles des États-Unis pour le traitement clinique des patients atteints de diabète de type 1 et de type 2. En raison des progrès technologiques, d’autres routes d’administration, comme les voies transdermique et orale (buccale et intestinale) en particulier, ont connu des progrès récents et pourraient devenir accessibles dans un futur proche. Combinées, ces voies d’administration, pourraient ainsi bientôt offrir aux patients diabétiques une alternative fiable, non invasive, efficace et plus physiologique au traitement insulinique par voie sous cutanée.

Mots-clés : Administration d’insuline • Voies alternatives • Insuline oculaire, orale, nasale, pulmonaire, inhalée • Revue générale.
Introduction

Optimal glycaemic control is the key to prevent long-term micro- and macrovascular complications of diabetes mellitus. Intensive insulin regimens that mimic physiological insulin secretion represent the best way to attain the goal of near-normoglycaemia. However in type 1 diabetes, only a few patients succeed in maintaining long-term HbA1c below 7% with complex and intensive insulin treatments involving multiple daily injections or continuous insulin infusion by pumps, sophisticated glucose monitoring, and meal glucose count. In patients with type 2 diabetes, insulin therapy is often initiated late in the course of the disease and intensification of treatment by insulin meet psychological resistance both by the patient and the physician. Consequently, more acceptable alternative routes of insulin administration have been searched for many decades, with the aim to avoid the burden of multiple subcutaneous injections and to improve insulin’s pharmacokinetics. Every imaginable route has been tested, but even if some of them are still promising like dermal, oral (buccal and enteral), only pulmonary inhaled insulin is currently approved by the FDA and marketed in the USA. Vaginal and rectal routes have been tested soon after the discovery of insulin. These routes have been tested again recently, an acidified Gelfoam® (an absorbable gelatine sponge) -based eye device, has been tested and the results suggest an efficient systemic absorption of insulin, at least in rabbits [4].

Anecdotals routes

OCular route

Insulin has been administered as eye drops to animals. When insulin is given alone at growing concentrations, no increase in systemic insulin level is observed and no toxicity is detectable [1]. Absorption is increased in animals when enhancers, like saponin, dodecylmaltoside, tretradecylmalto-side, fucicid acid or glycocholate, are added, but eye toxicity increased with the enhancer concentration [2, 3]. More recently, an acidified Gelfoam® (an absorbable gelatine sponge) has been tested and the results suggest an efficient systemic absorption of insulin, at least in rabbits [4].

Vaginal and rectal routes

These routes have been tested soon after the discovery of insulin but have met absorption problems through the mucosa, with very poor biodisponibility. Several classes of enhancers (bile salts, dihydrofusidate, cyclodextrins, surfactants and chelating agents) have been tested to promote the absorption, but with the induction of severe local reactions [5]. Moreover rectal route is subject to variability related to the intestinal transit. These routes do not seem to offer a real opportunity for the management of insulin-treated patients.

Transdermal route

Skin offers the advantages of an easy access and a very large surface area (1-2 m²). However, it represents an effective barrier that limits penetration of large, hydrophilic polypeptides, like insulin [6]. The upper layer, the stratum corneum, is responsible for this impermeability via its lipid-rich matrix [7]. Various methods have been tested to overcome the skin barrier and to allow insulin absorption. They can be separated into chemical (liposome and chemical enhancers) and physical methods (mainly iontophoresis and sonophoresis).

Chemical methods

Transport of molecules across the stratum corneum is slow and the mechanism appears complex. It is controlled by the predominant concepts which are partition, diffusion, and solubility. These parameters are to be targeted to improve the rate of absorption [8].

Chemical enhancers can increase permeability by increasing the partition coefficient of the drug, or increasing the thermodynamic action of the drug in the vehicle or modifying the nature of stratum corneum [9]. The incorporation of insulin in liposomes do not lead to systemic biological effect due to their size, which enables them to pass through the narrow pores (<30 nm) of the outer skin layer [6, 10, 11]. More recent studies have developed the concept of transfersomes which are ultraflexible, highly deformable, lipid vesicles incorporating surfactant molecules [12, 13]. Application of transfersomes including insulin (Transfusulin®) was reported to result in a transfer rate of approximately 50% of subcutaneous administration, and systemic normoglycaemia lasting at least 16 hours was achieved using a simple non-invasive epicutaneous administration of insulin in transfersomes [13]. These results, if confirmed by other studies, could imply a possible use of this route to cover basal insulin requirements. Preliminary studies using ethosomes or biphasic lipid-based vesicles have also shown possibilities of insulin transfer [14, 15].

Physical methods

Iontophoresis

Cathodal iontophoresis has been tested to increase transdermal insulin penetration. This technique uses electrically charged insulin molecules and a small electrical potential which can be manipulated to control the rate of insulin delivery [16]. It is poorly efficient, but can be improved by shaving the hairs, injuring the stratum corneum, or using monomeric insulin analogues [17, 18]. Nevertheless the amount of insulin transferred is insufficient to cover basal insulin requirements and long-term safety issues have not been assessed.

Sonophoresis

Low frequency ultrasound (20-160 kHz) (also called sonophoresis) can be used to increase transdermal insulin penetration applied as aqueous solution or mixed with a hydrogel [7, 19]. Decreases in blood glucose have been observed after application of low frequency ultrasound in animal and human studies [19-21]. This method seems feasible,
but needs further long-term studies. Other methods have been investigated, like pressure waves and electroporation, but they are still at a preliminary stage.

Up to now, results of studies assessing insulin administration through the skin as a possible treatment for diabetic patients remain limited. Combining chemical and physical methods needs further investigations.

**Per-oral (gastrointestinal) route**

Oral administration of insulin is a potentially attractive route, firstly because of its easy convenience, and secondly due to the portal drainage, then a more physiological delivery of insulin to the liver. However polypeptides, like insulin, are submitted to acidic degradation in the stomach and to enzymatic attacks in the small intestine. Moreover the gastrointestinal mucosa prevents absorption of large, hydrophilic peptides.

Several strategies, alone or in combination, have been developed to increase intestinal absorption of insulin. They include use of permeation enhancers (bile salts and fatty acids), associated or not, with enzyme inhibitors like aprotinin [22, 23], the use of liposomes, emulsions, mucoadhesive and polymer-based delivery systems [24, 25]. Previous studies performed with liposomes in animals, have shown mainly, a low absorption of insulin and variable decreases in blood glucose, depending on the physical and chemical composition of the liposomes [15]. Polymerisation, inclusion of insulin in an acryl biodegradable polyester, encapsulation into microspheres or in biocompatible nanocubicles have been tested [27-31]. These vehicles are degraded in the liver, releasing insulin in situ. All these strategies have achieved partial success and need further investigations.

A more promising formulation consists to modify the insulin molecule by a covalent attachment of amphiphilic low molecular weight oligomers. Hexyl-insulin monoconjugate 2 (HIM 2) is made of human recombinant insulin with an amphilic oligomer covalently bound to the free amino-acid group on the lys-β29 termination. This formulation improves solubility and stability of the molecule [32]. In healthy subjects [33], oral HIM2 suppresses endogenous glucose production and increases tissue glucose disposal, in a dose dependent manner. Absorption is rapid (peak plasma insulin is reached within 60 minutes and return to baseline in 120 minutes). The effects persist up to 240 minutes after administration. In type 1 diabetic subjects [34], a phase 1/2 clinical trial suggested that oral HIM2 is safe and may prove effective in controlling postprandial hyperglycaemia. In type 2 diabetic patients [35], a randomised-dose escalation study was performed: oral HIM2 and subcutaneous insulin provided comparable control of 2h-postprandial glycaemia and comparable 0-240min area under the curve (AUC), but HIM2 resulted in lower peripheral insulin concentration. These results confirm that oral HIM2 is absorbed though the portal circulation directly to the liver and then, could reproduce the physiological route of insulin secretion.

**Nasal route**

Nasal administration represents a potential route for insulin delivery due to the easy nose access, its high vascularisation and a relatively large surface (150 cm²) of absorption. However a very active mucociliary clearance mechanism, preventing prolonged contact of the drug with the mucosa, and the presence of proteolytic enzymes, do not favour a high biodisponibility [48]. Like buccal and intranasal routes, a number of factors influence bioavailability: type, volume and concentration of insulin and enhancers, physicochemical properties of the particles, frequency of administration, and indeed, the presence of various affections at the nasal level.

For several decades, numerous enhancers have been tested to improve insulin absorption with a local toxicity as lowest as possible. They include bile salts (1 to 4% sodium glycocholate and deoxycholate), fusidic acid salt

**Oral (buccal and sublingual ) routes**

The buccal mucosa offers the advantages of an easy accessibility and a large surface (100–200 cm²) for absorption. Moreover, it has little proteolytic enzyme activity and is a well vascularised tissue. However the continuous, but variable, saliva flow and the robust multilayered structure of the oral epithelium constitute a barrier to penetration of drugs [36].

Several strategies, alone or in combination, have been tested to improve buccal insulin absorption: use of absorption enhancers (bile salts, surfactants, fatty acids, alcohol, chelators) protease inhibitors, bioadhesive delivery systems (gels, films, patches), lipophilicity modifications (conjugation with polymers). All these studies, conducted in animals, have not shown a decrease of blood glucose greater than those obtained with 30% of the insulin dose administered intramuscularly. Furthermore, reproducibility seems poor [36-42].

A more promising technology has been developed by Generex Biotechnology Corporation (Toronto, Canada). It combines a liquid formulation (Oral-Lyn™) of recombinant human insulin and absorption enhancers and a propeller, the RapidMist® device, which sends small particles from an aqueous spray into the oral cavity. This allows rapid insulin absorption. Pharmacokinetics of insulin administered via this system has been evaluated in healthy subjects and in type 1 diabetic patients. The time to peak occurred at 25 minutes, and compared to subcutaneous regular insulin, a more rapid onset of action and a less prolonged hypoglycaemic action were observed. A dose-response relationship was noticed but pharmacokinetics were variable [45-47]. Short-term studies in patients with type 1 or type 2 diabetes, revealed that this oral insulin can be efficient in controlling postprandial glucose levels [46-48]. The oral insulin spray was generally well tolerated. This oral insulin system could represent an alternative to subcutaneous route, but needs further investigations on its reproducibility, tolerance and long-term efficacy in diabetic patients.
The kinetics profile of insulin administered by the nasal route has been evaluated in healthy subjects and in type 1 diabetic patients. These studies have shown a rapid increase of insulin concentration with a peak at 10-20 minutes, and a fast decrease of insulinemia (in about 2 hours). The bioavailability depends on the various factors already mentioned, and varies between 10 to 20% (with the exception of up to 45% in a preliminary animal study of insulin with chitosan gel). The effect is dose related, but with a huge variable inter-individual response [50, 51]. Nevertheless, this profile appeared potentially suitable for prandial insulin replacement, and then, short-term and long-term clinical studies have evaluated its efficacy in type 1 and type 2 diabetic patients [52-57]. The results were rather disappointing: in the short-term, glucose-lowering effect was too variable, and requiring high insulin doses given in one or more administrations on the long-term, HbA1c levels were not improved, and even mostly slightly deteriorated due to a too short duration of insulin action through this route of insulin delivery.

More recently, some new encouraging results have been obtained. In type 2 diabetic patients, a lyophilised formulation of insulin, using glycocholate as enhancer, was given before meals (associated to bedtime NPH insulin). Compared to twice daily subcutaneous NPH, similar glycaemic control was obtained [58]. In a 6-month study in type 1 diabetic patients, a gelified spray of insulin administered three times daily with NPH insulin twice daily, was as efficient as three subcutaneous injections [59].

Nevertheless, using this route, side-effects were important: nasal irritation was observed very frequently, immunogenicity or mitogens [50, 52, 55, 56, 59]. The development of a nasal insulin by the Novo-Nordisk company has been stopped, most likely due to these reasons. Up to now, the benefits/risk ratio of the nasal route does not seem favourable.

These review focuses on nasal insulin as an alternative route for insulin delivery in the treatment of diabetic patients. But recent studies have shown two different types of additional effects. First, nasal insulin alone, without enhancers, improves central nervous system function in healthy subjects and in Alzheimer-affected subjects [60, 61], without variation of peripheral insulinemia, probably via a direct nasal-to-brain effect. Secondly, prions insulin administered intranasally with anti-CD3, enhances remission from recent onset autoimmune diabetes in animals [62].

### Pulmonary route

Today, pulmonary inhaled insulin, seems the most promising alternative route of insulin delivery. The rationale for pulmonary administration is based on several facts: lungs provide a large, highly vascularised, potential absorption area (100–150 m²) (composed of bronchioles, alveoles ducts, and alveoles which represent 95% of the total absorption area). Alveoles are covered by a very thin (0.1–0.2 mm) monolayer of epithelial cells. There are few variations in mucus production, no mucociliary clearance, nor peptidases which represent barriers to absorption in other sites. The transport of molecules is not completely understood but for rather small molecules, like insulin, the predominant process is a juxtaglominal paracellular transport [63] when, for larger molecules, it is preferentially transcytosed.

Absorption is inversely related to molecular weight (<30 000 Da is better) and depends on MMAD (median mass aerodynamic diameter) which reflects the particle diameter and density [64]. Deposition is optimal in the deep lung for MMAD between 1.5–5 μm, larger particles remaining predominantly in the upper part of the respiratory tract, and smaller are mostly exhaled. Breathing characteristics have a major influence on intrapulmonary absorption [65] and all parameters influencing breathing will have to be studied to assess their influence on insulin absorption (smoking, asthma, lung diseases, exercise and patient’s ability to breath through inhaler devices).

Currently, four inhaled insulin systems have progressed to phase 3 clinical trials: AERx® Insulin Diabetes Management System (Aradigm Corp, Hayward, CA, USA and NovoNordisk, Copenhagen, Denmark) which delivers aerosol of human insulin; Exubera® system (Nektar Therapeutics/Pfizer Inc) which uses a dry powder formulation; Alkermes inhaler (Eli Lilly/Alkermes) delivers engineered human insulin powder; MedTon inhaler (Mannkind Corp., Danbury, CT, USA) delivers a powder of Technosphere®-associated human insulin. Other systems are less advanced, but will be described too. The Exubera® system was given marketing approval in 2006 by the US (FDA) and European (EMEA) health authorities for use in the treatment of type 1 and type 2 diabetic patients.

#### AERx® iDMS, developed by NovoNordisk

This system uses a liquid insulin formulation and expels a single dose of aerosol of fine insulin particles through a disposabale nozzle on a disposable dosage strip. The AERx®iDMS emits the aerosol by extruding the solution through the holes of the nozzle. Particles have a MMAD of 2.2 μm. It is a battery powered device utilising a microprocessor to guide electronically the user to the optimal breathing pattern (flow rate and depth of breath) [66, 67]. The system allows delivering metered dose of insulin and single unit increments. It has the size of a small book. As containing a liquid formulation, it requires cold storage.

Pharmacokinetics and bioavailability were studied in healthy subjects and type 1 diabetic patients [67-69]. The pulmonary delivery of insulin resulted in a rapid absorption (time to maximal concentration varying between 10 and
published yet. Inhaled insulin treatments have been studied in diabete patients. A proof-of-concept, randomised trial conducted in 107 patients with type 2 diabetes compared pre-meal inhaled or subcutaneous regular human insulin, in combination with bedtime NPH insulin during 12 weeks. No difference was observed between the two treatments for glycemic profiles after inhaled insulin administration was comparable to those observed after subcutaneous injections of regular insulin (intra-patient coefficient of variation for insulin AUC during 6 hours: 14% to 27% after inhaled insulin vs 19% after subcutaneous administration, and for glucose AUC: 21-30% vs 23% respectively. The variability was similar in smokers or elderly patients but higher in subjects with asthma [70-72, 74].

Up to now, a mid-term clinical study is available in diabetic patients. A proof-of-concept, randomised trial conducted in 107 patients with type 2 diabetes compared pre-meal inhaled or subcutaneous regular human insulin, in combination with bedtime NPH insulin during 12 weeks. No difference was observed between the two treatments for HbA1c, but fasting glucose was lower in the AERs®iDMS group. Frequency of adverse events was not significantly different, except a significant increase in insulin antibodies with inhaled insulin. Pulmonary assessment was normal [75]. The inhaled insulin was considered as well tolerated and provided excellent compliance. A multicentre, 24-month trial, initiated in 300 type 1 diabetic patients was designed to assess efficacy and safety of inhaled insulin, compared to subcutaneous injections of aspart insulin. To date, the results have not been published yet.

AIR (Advanced Inhalation Research), developed by Alkermes and Eli Lilly

The device is a simple, small, breath-activated system that uses capsules of dry-powder human insulin which are punctured before emission. The aerosol is made of large, porous particles, containing insulin associated with a biodegradable polymer matrix composed of phospholipids. The particles are relatively large (10-20 μm) but their MMAD is within 1 to 3 μm, and they have a reduced tendency to aggregate, thus facilitating dispersion [76]. Lung deposition of the particles (without insulin) has been studied in healthy subjects [77] with this system. Delivery was characterized by high and reproducible emitted doses, and high lung deposition (mean 51% of the total dose) with low inter- and intra-subject coefficient of variation across a various range of inspiratory flow rate. Pharmacokinetics and glucodynamics dose response of human insulin inhalation powder delivered by the AIR system were compared to subcutaneous lispro insulin in healthy subjects at various doses, using the euglycaemic clamp technique [78]. The time action profile was longer for inhaled vs subcutaneous insulin (time to return to basal level: 480 vs 360 minutes respectively) but both treatments showed rapid initial absorption (time to maximum concentration: 45 minutes), similar overall pharmacokinetics AUC and glucose lowering effect. Inhaled insulin doses equivalences were shown to be 2.6 mg for 6 IU, 5.2 mg for 12 IU and 7.8 mg for 18 IU of lispro insulin. Tolerance was considered to be excellent. A clinical, randomised, cross-over study [79] performed in patients with type 1 diabetes has compared inhaled to subcutaneous (lispro and regular) as pre-prandial insulin associated with glargine in a basal-bolus regimen. However, it has to be noticed that metabolic targets were not stringent. At the end of the 12-week treatment periods, HbA1c was comparable and sub-optimal in the two groups (inhaled vs subcutaneous: 7.95 vs 8.06%). Fasting blood glucose was lower with inhaled insulin. Safety profiles were comparable, except for the incidence of nocturnal hypoglycaemia which was higher with inhaled insulin. These latter facts need further explanations.

Exubera®, developed by Nektar/Pfizer

Exubera® was granted marketing approval by health authorities (EMEA in Europe and FDA in the US) in January 2006, for the treatment of type 1 (in association with basal insulin) and type 2 diabetes.

The device uses insulin powder formulation, which consists of recombinant human insulin (60%) and excipients (mannitol, glycine, sodium and nitrate). The powder is packed in blister packs, each one containing 1 or 3 mg of insulin (about 28 and 84 IU) equivalent to 3 IU and 9 IU of subcutaneous insulin respectively [80, 81] which represents a 10% relative activity. The blister is inserted into a slot at the base of the device. Activation leads to compressing trapped air, puncturing the blister and releasing air through the blister at high velocity. Insulin particles (MMAD approximately 3 μm) are aerolised into an inhalation chamber. Then, the subject inhales the respirable cloud with a full slow breath. The device is 23 cm long, but when it is folded, it has the size of devices used for asthma. Pharmacokinetics of inhaled insulin has shown a peak at about 55 minutes and a more rapid return to basal level than regular subcutaneous insulin [81]. Pharmacodynamics of Exubera® inhaled insulin was compared to regular insulin and insulin lispro in healthy subjects. Inhaled insulin has the fastest onset of action, a comparable time to maximal effect to insulin lispro, a maximal metabolic effect and duration of action comparable to regular insulin [82]. Reproducibility evaluated in type 2 diabetic
patients is similar to subcutaneous insulin [83]. Smoking influences inhaled insulin profile, the peak occurs earlier (31 vs 53 minutes) and its magnitude as well as the total insulin absorption (AUC 0 to 6 hours) are greater, these changes being partly reversible with smoking cessation [84]. Safety and efficacy have not yet been established in patients with asthma, chronic obstructive pulmonary disease (COPD) or acute respiratory infection.

The clinical metabolic efficacy has been evaluated in approximately 3000 patients with type 1 or type 2 diabetes. In patients with type 1 diabetes, a proof-of-concept, open-label, 3-month randomised study compared inhaled insulin given 10 minutes before meals associated with ultralente insulin at bedtime, and two or three subcutaneous injections of regular and NPH insulin at bedtime [85]. At the end of the study, glycæmic control evaluated by HbA₁c was similar in the two groups (7.9% and 7.7% respectively). Glycaemic profiles after a standardised meal were comparable for both treatments at the beginning and at the end of the trial, and metabolic side-effects (hypoglycaemia, weight gain) were similar. Two 6-month randomized phase 3 studies, compared inhaled with subcutaneous pre-meal regimens. The first one [86] compared pre-meal inhaled to regular subcutaneous insulin and twice daily NPH insulin injections (conventional treatment) in 335 type 1 diabetic subjects. Mean decrease in HbA₁c was comparable with the two treatments. A greater reduction in fasting and postprandial glycaemic reduction were comparable in the two groups, but fasting glycaemia was lower in the inhaled insulin group. Hypoglycaemia was slightly lower with inhaled insulin. The second study [87] used the same design, but compared pre-meal inhaled vs subcutaneous regular (but not analogue) insulin, in 568 type 1 diabetic patients receiving NPH insulin twice daily in a basal-bolus regimen, but with conventional therapeutic objectives. HbA₁c and 2-h postprandial glycaemic reduction were comparable in the two groups, but fasting glycaemia was lower in the inhaled insulin group. The overall hypoglycaemia rate was slightly less (inhaled vs subcutaneous: 9.3 vs 9.9 episodes/patient-month) but severe hypoglycaemia frequency was comparable (inhaled vs subcutaneous: 5.5 vs 4.7 events/100 subject-months). No clinical study has been published yet, comparing inhaled insulin with intensified subcutaneous regimens using insulin analogues and with stringent fasting and postprandial glucose targets.

In type 2 diabetic patients, one proof-of-concept trial and several phase 3 studies assessed efficacy of Exubera® at different stages of the disease and versus different oral antidiabetic treatments. In the first one [81], metabolic efficacy (HbA₁c, glucose profiles after a standardised meal and frequency of hypoglycaemia) were comparable. A randomised study [88] conducted in type 2 diabetic subjects with diabetes control failing off on diet and exercise, compared pre-prandial inhaled insulin alone to rosiglitazone twice daily and showed better metabolic control with inhaled insulin. Another randomized study [89], evaluated Exubera® alone vs Exubera® and oral antidiabetic drugs only. Metabolic control at the end of the study was significantly improved in patients receiving Exubera®. In a 6-month study [90] with a design similar to the trial in type 1 diabetic patients previously described [82], the decrease in HbA₁c was comparable with inhaled or subcutaneous regimens, but more patients with inhaled therapy reached an HbA₁c lower than 7%.

Non metabolic side-effects (pulmonary consequences, immunogenicity), patients satisfaction and costs, have been studied, although with various approaches, with all inhaled insulin delivery devices, but studies conducted with Exubera® are clearly at a more advanced stage. However, all these concerns are expected (or have proved) to be similar with any inhaled insulin.

In most studies, pulmonary functions were reported to remain stable, although a decrease in carbon monoxide (CO) diffusing capacity was noted [86, 90]. Mild to moderate cough was reported throughout all studies, but seems to decrease over treatment periods [86-90]. FDA recommends baseline pulmonary function testing prior to initiation of treatment and every year [80]. The use of Exubera® is contraindicated in patients with lung disease, and in patients who smoke or discontinued smoking less than six months prior to initiating it. Exubera® treatment is not recommended in patients with chronic pulmonary disease (asthma, COPD) due to its non-established efficacy and safety in these diseases.

Exubera® (like other inhaled insulin) induces a higher increase of insulin antibodies compared to subcutaneous treatment. This increase does not seem to lead to detectable metabolic consequences [91, 92].

In phase 2 and 3 clinical trial, Exubera® (like other inhaled insulin), was associated with a higher satisfaction of patients towards their treatment than subcutaneous injections [85-90]. Moreover a specific 1-year study [93] addressed specifically patients satisfaction and demonstrated a greater satisfaction with inhaled insulin. Furthermore, this route of treatment administration has been shown to improve the acceptance of insulin treatment by type 2 diabetic patients [94].

Studies focusing on costs associated with inhaled insulin treatment compared to conventional treatments of diabetes (oral antidiabetic agents and/or subcutaneous insulin regimens) are not available yet, nor cost/effectiveness data. Inhaled insulin treatment is expected to be significantly more expensive than injectable insulin, due to the higher amount of inhaled insulin required for equivalence to subcutaneous administration (a 10% bioavailability for inhaled vs subcutaneous administration), the price of the device and its related furnitures. However this has to be balanced with a better acceptance of insulin treatment via this route, which could imply a wider use of insulin in type 2 diabetic patients (reducing the production costs) and less long-term diabetic complications through an earlier and better diabetes control and prevention. However, all these considerations await further studies [95].
Alternatives routes of insulin delivery

**Aerodose® (Aerogen Inc/Nektar Therapeutics)**

Aerodose® is a system activated by breath which uses a liquid insulin formulation aerosolised in small droplets. Pharmacokinetics and pharmacodynamics studies [96, 97] have shown a time to peak insulin level shorter after insulin inhalation than after regular subcutaneous insulin (60–97 minutes vs 168–237 minutes) and an onset of action and a peak metabolic effect occurring earlier with inhaled insulin. Reproducibility was similar with inhaled or subcutaneous insulin.

**Technosphere® Insulin (Mannkind Corporation)**

Technosphere® insulin is a kind of lattice containing a dry-powder formulation of crystallized insulin in gelatine capsules. The insulin delivery mechanism uses a high-impedance inhaler with a powder deagglomeration system. Pharmacokinetics and pharmacodynamics studies have shown a very fast absorption (time to peak insulin level: 12–14 minutes, time to maximum metabolic effect: 20–40 minutes) and a short duration of action (2 to 3 hours). Bioavailability was proportional to the administered dose and the biopotency was around 15% [98]. This formulation seemed to be well tolerated and is currently entering phase 3 studies.

**Spiro System (Dina Pharmacy Inc/Elan Corporation)**

Spiro System provides a dry-powder insulin formulation encapsulated in blister-disks via a breath-activated inhaler. After inhalation, peak insulin level was observed at 70 minutes and a dose-response relationship was observed [99].

**Conclusion**

More acceptable, painless routes of insulin delivery have been searched for many years to avoid the burden of insulin injections to diabetic patients and thus, alternative routes of insulin delivery is already a long time story [review in 100-102]. Interest in these alternative routes has grown up over the last few years, in parallel to progress in insulin formulations and advanced technology of delivery systems, as illustrated by the large number of excellent reviews on these topics [103-109].

At the time being, the most promising alternative to subcutaneous insulin injections is represented by insulin inhalation via the pulmonary route. Among the number of various inhaled insulin systems in development, the first one, Exubera®, was given approval for use in the treatment of type 1 and type 2 diabetic patients, by the FDA and the EMEA in January 2006; most of the other systems being currently in phase 2/3 studies. Pre-prandial inhaled insulin has proved to be as efficient as conventional treatments/regimens using subcutaneous insulin injections in type 1 and type 2 diabetic patients. Inhaled insulin seems to be well tolerated and to improve patients’ acceptance of insulin treatment, which could lead to an improved diabetes control and prevention of long-term diabetic complications. However, comparisons with intensified insulin regimens using stringent metabolic control goal (HbA1c) are still lacking, as well as long-term studies on cost-effectiveness and pulmonary safety.

Development of other alternative, painless, routes of insulin delivery are also in progress, and oral routes (intestinal and buccal) have recently shown very interesting advancements. Furthermore the intestinal route (via hepatoportal drainage) has the potential advantage of a more physiological administration.

Today, complete (basal and prandial) replacement of subcutaneous insulin treatment by alternative routes is not available yet, and likely, would require a combination of different approaches. But non subcutaneous pre-prandial insulin treatment has become available with the health authorities approval of pulmonary inhaled insulin for treatment of type 1 and type 2 diabetes, and this may be the beginning of a lighter burden for diabetic patients. The exact place of these new routes of insulin administration in the broad range of currently approved diabetes treatments deserves further research.

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