

# Efficacy and safety of inhaled insulin in the treatment of diabetes mellitus

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## ABSTRACT

Many patients with diabetes mellitus view subcutaneous injections of insulin as a daily burden. Pulmonary delivery of insulin offers an alternative route of administration and may as such improve diabetes treatment. Inhaled insulin provides a rapid absorption of insulin, but with low bioavailability. Phase III clinical trials in type 1 and type 2 diabetes have disclosed clinical equivalence between three inhaled insulin products (Exubera, AERx iDMS, and HIIP) and regular human insulin, both in terms of glycaemic control and hypoglycaemic risk. Inhaled insulin cannot be used to replace basal insulin requirements. The most commonly reported adverse effects of inhaled insulin are cough and insulin antibody formation, the clinical significance of which is uncertain. No or minimal deterioration in pulmonary function parameters have been recorded, although studies were typically of short duration. Patients participating in inhaled insulin trials generally expressed satisfaction with the product and chose to remain on it. The availability of inhaled insulin may increase willingness in type 2 diabetic patients to consider insulin therapy. More studies of longer duration are required to determine (pulmonary) safety and cost-effectiveness of inhaled insulin, and to disclose which patients may benefit the most.

## KEYWORDS

Diabetes mellitus, glycaemic control, hypoglycaemia, inhaled insulin, treatment

## INTRODUCTION

More than 80 years ago, Banting and Best introduced therapeutic insulin into clinical practice. They were able to extract the hormone and inject it into a 14-year-old boy diagnosed with type 1 diabetes, saving him from premature death.<sup>1</sup> Currently, a wide range of injectable insulin products are available for the treatment of diabetes, which are being used by millions of patients with type 1 and type 2 diabetes worldwide. These products include short- and immediate-acting preparations to be used during mealtimes, intermediate- and prolonged-acting agents intended to replace basal insulin requirements, and premixed formulations. Despite these various profiles, it has proved virtually impossible to replicate the physiological pattern of endogenous insulin secretion to maintain near-normal levels of glycaemia. Consequently, microvascular and macrovascular complications remain highly prevalent in both type 1 and type 2 diabetes.<sup>2-4</sup> In addition, despite advances in the development of smaller needles and patient friendly pen-injector devices to allow better tolerability of subcutaneous administration, injection of insulin is still viewed as a complicated and painful procedure.<sup>5</sup> The burden of three to six insulin injections daily may lead to avoidance to self inject, even in the absence of overt needle phobia.<sup>6</sup> Attempts to develop noninvasive routes for insulin administration emerged soon after the introduction of insulin. Degradation by the acidic environment of the stomach or by digestive enzymes in the upper gastrointestinal tract, active mucociliary clearance and presence of proteolytic enzymes in the nasal cavity, and the relative impermeability of the skin have precluded successful delivery by oral, intestinal, intranasal, and transdermal routes.<sup>7</sup> None of these obstacles apply to pulmonary delivery of insulin. On the contrary, the lungs appear perfectly equipped for the absorption of small peptides such as insulin. The surface area of the alveoli

measures ~140 m<sup>2</sup> (corresponding to half a tennis court), and is lined by a very thin (0.1-0.2 μm), richly perfused, highly permeable monolayer of epithelium. In addition, the lungs are highly immunotolerant and largely lack mucociliary transport.<sup>8</sup> Interest in delivering insulin through the pulmonary tree originated in the 1920s.<sup>9</sup> In 1971, it was shown that inhalation of insulin resulted in a prompt increase in plasma immunoreactive insulin and a reduction in blood glucose levels in healthy and diabetic subjects.<sup>10</sup> Better understanding of aerosol dynamics and particle properties has contributed greatly to the current development of inhaled insulin preparations. Several pharmaceutical companies have collaborated with pulmonary drug delivery companies to develop an inhaled insulin product and corresponding inhalation system (table 1). At least one inhaled insulin preparation will soon be released on the (Dutch) market. The objectives of this review are to provide an overview of pulmonary insulin preparations in development, to discuss pharmacokinetics and safety of inhaled insulin, and – specifically – to critically evaluate results of clinical trials performed with inhaled insulin.

## PHARMACOKINETICS

Several factors affect the pulmonary delivery of inhaled insulin. These include the efficiency of the inhaler, the size of the particles in the aerosol, and the breathing pattern. The efficiency of the inhaler device reflects the percentage of drug emitted from the device by correct inhalation, which is usually 80 to 95% for dry-powder inhalers, but can be as low as 20 to 30% for liquid nebulisers.<sup>11</sup> The optimal

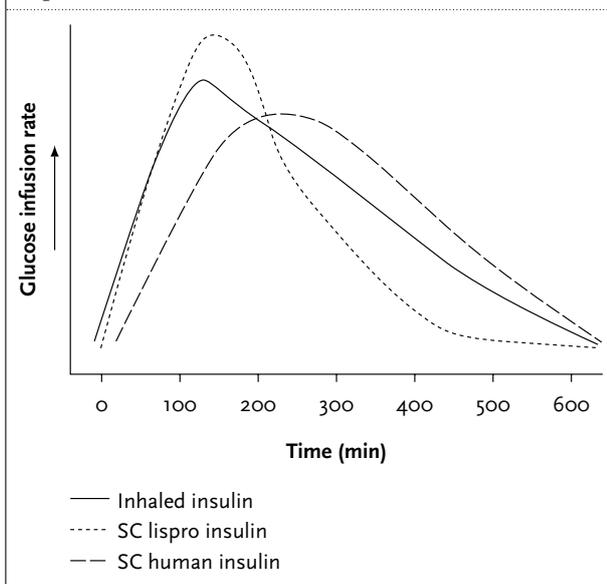
particle size for deep alveolar deposition is an aerodynamic diameter (a function of the geometric diameter and mass density) of 1 to 3 μm; larger particles, especially >10 μm, are primarily deposited in the upper airways or oropharynx, whereas smaller particles are mostly exhaled. The aerosol is best inhaled by slow inspiration with a large tidal volume. A good pulmonary function is a prerequisite for inhalation therapy. Performing a breath-hold of two to six seconds at the end of inspiration can improve collection efficiency of the alveolar region. Forced inspiration, however, has an adverse effect on alveolar deposition and leads to particle loss in the orolaryngeal region.<sup>12</sup> Transport of insulin across the alveolar wall probably occurs by a paracellular process, although the exact process is still incompletely understood.<sup>11</sup> There is evidence that only 20 to 40% of insulin deposited in the lung reaches the circulation. The remainder undergoes cytosolic biodegradation or exits the lung via the mucociliary escalator.<sup>11</sup> Smoking, both acutely and chronically, enhances the absorption of insulin. Smokers were found to have more than threefold higher peak insulin levels upon inhalation of a standard insulin dose, resulting in hypoglycaemia.<sup>13</sup> Under optimal conditions, bioavailability of inhaled insulin in nonsmokers is approximately 8 to 12%. Absorption of inhaled insulin occurs rapidly. The time to reach maximum insulin concentration and glucose-lowering effect is similar to that of subcutaneous short-acting insulin analogues and shorter than that of subcutaneous regular insulin (figure 1). The duration of action of inhaled insulin is four to six hours, slightly longer than short-acting analogues and slightly shorter than subcutaneously injected regular insulin.<sup>14</sup> These pharmacokinetic characteristics make inhaled insulin suitable as mealtime insulin.

**Table 1. Inhaled insulin products currently under development**

Developer	Partners	Type of product and inhaler	Trade name
Nektar therapeutics	Pfizer	Dry powder Passive inhaler	Exubera®
Aradigm	Novo Nordisk	Liquid aerosol Microprocessor-controlled inhaler	AERx® iDMS
Alkermes	Eli Lilly	Dry powder Passive inhaler	HIIP®
Aerogen	-	Liquid aerosol Passive inhaler	Aerodose®
Pharmaceutical Discovery Corporation	Mannkind	Dry powder microparticles Passive inhaler	Technosphere®
Dura Pharmaceuticals	-	Dry powder Electromechanical inhaler	Spiros®
Microdose Technologies	Elan Corporation	Dry powder	Microdose DPI®
Kos Pharmaceuticals	-	Dry crystals Propellant inhaler	Unknown
BioSante Pharmaceuticals	-	Coated dry particles	Bio-Air®
CoreMed	-	Liquid aerosol	Alveair®

HIIP = human inhaled insulin powder.

**Figure 1.** Glucose infusion rate in healthy individuals after inhalation of insulin, subcutaneous injection of regular insulin, and subcutaneous injection of insulin lispro<sup>14</sup>



## PRODUCTS

Table 1 provides an overview of the pulmonary insulin delivery systems that are currently being studied. Most systems are being developed by a joint venture between the manufacturer of inhalation devices and a pharmaceutical company that produces the insulin preparations. The insulin preparation is either a dry-powder or a liquid formulation. Dry-powder formulations have superior room-temperature stability, can deliver more insulin per inhalation, and are less prone to microbial growth, whereas liquid aerosol formulations are less susceptible to the influence of external humidity on dispersion. The products are in various stages of development, three of which have been tested in phase III clinical trials. The results of these trials will be discussed in more detail.

### Exubera

The most thoroughly investigated inhaled pulmonary insulin system is Exubera, which consists of a dry-powder formulation with regular insulin (approximately 60%) and stabilisers, primarily mannitol, packaged in 1 and 3 mg blisters that contain 28 and 84 units of insulin, respectively. After placing a blister in the slot of the inhaler, the insulin is dispersed into an aerosol in a spacer reservoir, from which it can be subsequently inhaled. The bioavailability of the Exubera system is 9% and the biological efficiency (i.e. the blood glucose lowering effect) is 10 to 11% compared with subcutaneously injected insulin.<sup>14</sup> Thus, 1 mg of Exubera is comparable with approximately 3 units of subcutaneous insulin.

Studies that reported on the clinical efficacy of Exubera in type 1 diabetes include one small 12-week proof of concept study<sup>15</sup> and two larger randomised trials (follow-up six months),<sup>16,17</sup> involving 735 patients in total. In these studies, the experimental group received inhaled insulin at mealtimes in combination with either subcutaneous ultralente insulin once daily or NPH insulin twice daily. The comparator group either continued their subcutaneous insulin regimen of two to three insulin injections<sup>15,16</sup> or received mealtime regular insulin in combination with NPH insulin twice daily.<sup>17</sup> Insulin analogues were not used in either of these studies. Basal insulin replacement therapy was only identical in the experimental and comparator group in one study.<sup>17</sup> The mean daily dose of inhaled insulin ranged from 9.6 to 12.4 mg at initiation and increased slightly during the study to 10.8 to 14.2 mg.<sup>16,17</sup> From these data it can be calculated that, on average, the majority of patients used at least two to three blisters to meet insulin requirements at mealtimes. Inhalation therapy was found to be clinically equivalent to subcutaneous insulin treatment in all three studies. Over six months of treatment, HbA<sub>1c</sub> values fell by 0.2 to 0.3% in patients randomised to inhaled insulin and by 0.16 to 0.4% in patients randomised to subcutaneous insulin, differences that obviously were not statistically significant.<sup>16,17</sup> Fasting plasma glucose values decreased slightly more in the inhaled insulin treatment arms than with comparator treatment in both studies.<sup>16,17</sup> In type 2 diabetic patients inadequately controlled by diet, treatment with inhaled insulin resulted in better glycaemic control than with rosiglitazone.<sup>18</sup> After three months, the goal of HbA<sub>1c</sub> <7% was achieved by 44% of patients in the inhaled insulin group compared with 8% in the rosiglitazone group. However, the study has been criticised for its relatively short duration, since rosiglitazone may take longer to become fully effective. Inhaled insulin resulted in more weight gain than rosiglitazone treatment (1.9 vs 0.8 kg), an observation possibly related to the higher rate of hypoglycaemia (0.7 vs 0.05 per patient-month) or faster achievement of good glycaemic control. In patients inadequately controlled by diet and a single oral agent (either metformin or a sulphonylurea derivative), addition of inhaled insulin was as good as an addition of a second oral agent from the alternative group.<sup>19</sup> Patients who were poorly controlled by two oral agents were found to benefit from switching to inhaled insulin monotherapy, but addition of inhaled insulin on top of oral therapy was even better.<sup>20</sup> An HbA<sub>1c</sub> value below 7% was achieved by 32% of the patients in the combination group compared with 17 and 1% in the inhaled insulin and oral agent monotherapy groups, respectively. In insulin-treated type 2 diabetic patients, the combination of inhaled insulin at mealtimes and ultralente insulin subcutaneously resulted in similar improvement of glycaemic control as a subcutaneous regimen consisting of two to three injections of regular and NPH insulin.<sup>21,22</sup>

The daily dose of inhaled insulin averaged 15 mg after six weeks and 16.6 mg after 24 weeks of treatment. Weight gain did not appear to occur with inhaled insulin, whereas the subcutaneous regimen was associated with almost 1.5 kg increase in weight.<sup>22</sup>

#### AERx iDMS

The AERx iDMS delivery system was developed as a device for the pulmonary administration of liquid aerosols of insulin. The inhaler is breath activated and only releases the insulin when inspiratory flow is sufficient, in order to minimise intra-subject variability due to patient technique. The insulin is packaged in strips that contain an amount of insulin corresponding to approximately 1 unit subcutaneously. The bioavailability and pharmacological efficiency of the AERx iDMS system in type 1 diabetic patients were 12.9 and 12.7%, respectively.<sup>23</sup> In nondiabetic subjects, upper respiratory tract infections did not affect the pharmacological efficacy of AERx.<sup>24</sup> In a small, randomised, open-label study in 107 insulin-treated type 2 diabetic patients, the clinical effect of premeal use of AERx was compared with subcutaneous regular insulin, against a background of NPH insulin once daily.<sup>25</sup> After 12 weeks, HbA<sub>1c</sub> fell by 0.69 and 0.77% in the inhaled insulin and subcutaneous insulin groups, respectively. Fasting blood glucose levels tended to be lower with inhaled insulin (7.04 vs 7.78 mmol/l,  $p=0.08$ ), but prandial increments were similar. Patients in the inhaled insulin group received, or required, more contacts and more time per contact for instruction than the patients from the comparator group.

#### Human inhaled insulin powder

Advanced inhalation research developed large porous particles of low mass that consist of a biodegradable polymer matrix that contains fast-acting human insulin. Future developments might involve production of a sustained-release formulation. The capsules contain human inhaled insulin powder (HIIP) as a dry powder in two dose strengths of either 0.9 mg or 2.6 mg, equivalent to 2 or 6 units of subcutaneous insulin, respectively.<sup>26</sup> A preliminary study involving 137 type 1 diabetic patients reported that premeal use of this inhaled insulin in combination with glargine was clinically equivalent to a subcutaneous regimen of premeal regular or lispro insulin and glargine.<sup>27</sup> However, as this study was designed to show noninferiority of inhaled insulin, its efficacy to reach glycaemic targets was not tested.

#### Other products

Technosphere insulin is a dry-powder pulmonary insulin packaged in microparticles to which an absorption enhancer is added. The particles rapidly dissolve in the alveolar space to release insulin. The absorption of Technosphere insulin occurs faster and more efficiently

than the other inhaled insulin products, with respect to time-to-peak insulin concentration (13 minutes), time-to-maximal effect (39 minutes), and bioavailability relative to subcutaneous (26%) and intravenous insulin (19%).<sup>28</sup> Clinical studies are awaited. Aerodose is a novel liquid pulmonary insulin with a relative bioavailability of 21% in type 2 diabetic patients,<sup>29</sup> yet its development has been halted. Other inhaled insulin formulations under development are ProMaxx, Kos insulin and Spiros.

## SAFETY

#### Hypoglycaemia

Several studies have reported a slightly lower relative risk for any hypoglycaemic event with the use of inhaled vs subcutaneous insulin, ranging from 0.69 to 0.96, both in type 1 and type 2 diabetes.<sup>16,22,25</sup> These data are at odds with studies reporting a doubling of the incidence of severe hypoglycaemic events (6.5 vs 3.3 events per 100 patient-months)<sup>17</sup> and a higher incidence of nocturnal hypoglycaemia<sup>27</sup> in type 1 diabetic patients randomised to inhaled insulin compared with those randomised to subcutaneous treatment. A Cochrane systematic review on six randomised controlled trials concluded that, overall, there was no or little difference in hypoglycaemic risk between inhaled and subcutaneous insulin.<sup>30</sup>

#### Pulmonary adverse events

Concern has been raised that the alveolar deposition of insulin may have adverse pulmonary effects, because of insulin's vasodilator and growth promoting characteristics. To date, however, pulmonary oedema or malignant tumours have not been reported in association with inhaled insulin use. In general, inhaled insulin is well tolerated. The main adverse event reported by users of dry-powder inhaled insulin formulations is cough. In the trials with Exubera, 8 to 27% of patients on inhaled insulin vs 1.5 to 7% of patients on comparator treatment reported cough,<sup>16-18,20,31</sup> usually occurring directly following inhalation and characterised as mild to moderate. Shortness of breath was also more prevalent in the inhaled insulin groups than in the control groups. However, these adverse events rarely lead to discontinuation of treatment.<sup>32</sup> Neither cough nor shortness of breath was reported in excess by patients randomised to liquid inhaled insulin compared with subcutaneous insulin.<sup>25</sup>

Pulmonary function tests have revealed a slightly greater reduction in both forced expiratory volume in 1 second (FEV<sub>1</sub>) and in monoxide diffusing capacity (DL<sub>CO</sub>) in patients allocated to inhaled insulin treatment than in those of the comparator groups. The differences occur in the first weeks, are small and not progressive. In a study among type 2 diabetic patients, the difference in

FEV<sub>1</sub> and DL<sub>CO</sub> between inhaled insulin treatment and control treatment decreased gradually between week 24 and 104, and was no longer discernible 12 weeks after discontinuation.<sup>33</sup> In addition, annualised declines of FEV<sub>1</sub> and DL<sub>CO</sub> during a four-year extension study did not appear to continue in 159 type 1 and type 2 diabetic patients who had chosen to continue inhalation therapy or to switch from comparator treatment after a randomised clinical trial.<sup>34</sup> These data do not exclude long-term pulmonary side effects of inhaled insulin, since patients at high risk for pulmonary disease (e.g. smokers) have been excluded from participation in clinical studies. Moreover, pulmonary function appears to deteriorate with worsening glycaemic control<sup>35</sup> and structural pulmonary abnormalities have been suggested to parallel the development of classical microvascular complications in diabetes, both of which raise concern with respect to inhaled insulin treatment.<sup>36</sup> Clearly, much longer follow-up data are required to establish pulmonary safety for a product destined to be inhaled for a lifetime of diabetes.

#### Insulin antibody response

In all studies, inhaled insulin was found to produce larger insulin antibody responses, mainly of IgG class, than subcutaneous insulin, irrespective of formulation. Pooled data from studies on Exubera revealed a relationship with prior therapeutic insulin exposure. Median antibody responses increased from 3 to 31% in patients with type 1 diabetes, and from less than 3% to 13 and 6% in insulin-treated and insulin-naïve type 2 diabetic patients, respectively.<sup>37</sup> The peak in antibody responses was observed after 6 to 12 months of treatment and then stabilised in all groups. Use of AERx or other inhaled insulin products was associated with similar excess in insulin antibody responses.<sup>25</sup> The clinical relevance of this observation has not yet been clarified. So far, no relation has been found between presence of insulin antibodies and insulin dose requirements, fasting blood glucose levels, glycaemic control, hypoglycaemia incidence, or adverse events.<sup>37</sup>

#### PATIENT PREFERENCES

In terms of quality of life and treatment satisfaction, the development of smaller and sharper needles and pen-injector systems may have benefited patients at least as much as the biochemical advances in the production of injectable insulins. Nevertheless, many patients welcome a noninvasive alternative. Type 2 diabetic patients failing on oral hypoglycaemic agents (mean HbA<sub>1c</sub> 9.1%) were almost three times as likely to choose (additional) insulin therapy if inhaled insulin would have been available than if they could only select standard insulin therapy.<sup>38</sup> In randomised trials that included assessment of treatment satisfaction,

patients allocated to inhaled insulin ended up being more satisfied (with insulin treatment) than patients allocated to subcutaneous insulin.<sup>15-17,22</sup> After successful completion of one of two 12-week randomised controlled trials, 85% of (type 1 and type 2 diabetic) patients randomised to inhaled insulin chose to continue treatment and 75% of patients who had received subcutaneous insulin chose to switch to inhaled insulin. After one year, treatment satisfaction was universally greater in patients treated with inhaled insulin than in patients treated subcutaneously, irrespective of their initial treatment allocation in the parent studies.<sup>39</sup> It was concluded that diabetic patients prefer inhaled insulin to subcutaneous insulin. However, interpretation of the data is critical when the comparator treatment consists of continuation of existing therapy. This is illustrated by studies showing that the magnitude of treatment satisfaction is determined mainly by the level of (improvement in) glycaemic control, whereas this parameter did not differ between inhalation insulin and comparator treatment arms.<sup>40,41</sup> An explanation for this seemingly paradoxical phenomenon is that patients allocated to inhalation insulin might have been tempted to attribute glycaemic improvement to the novel experimental agent (possibly enhanced by enthusiasm from their healthcare providers), whereas those allocated to continuation of subcutaneous insulin might have attributed improvement to a study effect. In turn, it could be speculated that increased motivation to comply with dietary instructions explained the absence of weight gain and the lower fasting plasma glucose levels in the inhaled insulin groups.

#### FINANCIAL ASPECTS

At the moment, none of the companies have disclosed the price of their product. Due to the high insulin content and costs of development, it is anticipated that inhaled insulin will cost considerably more than currently available subcutaneous insulin preparations, including insulin analogues. Moreover, extra costs are to be expected due to the need for pulmonary function monitoring. The supposed greater convenience and acceptability of inhaled insulin compared with subcutaneous insulin has been suggested to enhance willingness in type 2 diabetic patients to use insulin for optimisation of glycaemic control, thereby reducing health care cost.<sup>38</sup> However, a study on cost effectiveness of inhaled insulin has not yet been performed. The Real World Trial, which aims to investigate the effect of introducing inhaled insulin to clinical practice on health benefit and is due to report in 2007, may provide some answers on this issue.<sup>42</sup> If inhaled insulin turns out to be the blockbuster it is assumed (or hoped) to become, a costly boost of the production capacity of therapeutic insulin is likely to be required.

## CONCLUSION AND PERSPECTIVES

Inhaled insulin is the first noninvasive alternative to subcutaneous insulin administration that is to be marketed this year. Despite the relatively low bioavailability of most products, pulmonary administration of insulin provides clinically effective plasma insulin levels and sufficient blood glucose lowering. Its pharmacological profile resembles that of subcutaneous immediate-acting insulin analogues, making inhaled insulin suitable for premeal administration. Clinical studies in type 1 and type 2 diabetic subjects indicate equivalence between inhaled insulin-based regimens and subcutaneous insulin-based regimens with respect to glycaemic control and incidence of hypoglycaemic events, provided that basal insulin requirements are met. However, comparator treatment often involved a suboptimal regimen, whereas inhaled insulin was given in a basal-bolus regimen, making comparisons difficult. Despite its pharmacological profile, a randomised controlled trial comparing inhaled insulin with immediate-acting analogues has not yet been published. Inhaled insulin monotherapy may be as good as or better than oral agents in achieving glycaemic targets in type 2 diabetic patients who fail on diet or single-agent oral therapy. The combination of the two is better than either treatment alone.

Long-term safety remains an issue of concern. Although the absence of clinically relevant pulmonary adverse events with use of inhaled insulin is encouraging, data were obtained over relatively short follow-up and in patients without risk factors for pulmonary disease. Smokers and patients with obstructive lung disease have not been enrolled in inhaled insulin studies. More and longer-term studies are required. These may also disentangle the immunogenicity of inhaled insulin, for instance to determine whether insulin antibodies are able to cross the placenta.

In the absence of a clear clinical benefit on subcutaneous insulin, there is currently no indication for inhaled insulin treatment in patients with type 1 or insulin requiring type 2 diabetes mellitus. Nevertheless, it is well known that the switch to insulin therapy is often delayed in type 2 diabetic patients poorly controlled by oral treatment and lifestyle changes alone, despite the obvious advances with respect to glycaemic control and risk of complications. High acceptance of inhaled insulin might encourage these patients to switch to insulin therapy at an earlier stage, but this needs to be confirmed in clinical practice. In addition, the availability of inhaled insulin may benefit the management of selected patient groups, such as those with severe needle phobias, patients with recurrent local complications of subcutaneous insulin (such as skin infections or skin contact allergies), and patients with dermatological ailments or severe lipodystrophy for whom finding a suitable injection spot may be difficult. These patients should not smoke (in the past six months),

have ongoing pulmonary disease or reduced pulmonary function, be pregnant, or be younger than 18 years of age. Caution should be exercised in patients with microvascular complications and in those with poor glycaemic control. Whether inhaled insulin will be cost-effective remains an important, yet unresolved, issue.

## NOTE

B.E. de Galan and C.J. Tack have participated in a phase II clinical trial with Technosphere insulin. R.J. Heine is a member of the International Advisory Board of Pfizer Inc.

## REFERENCES

1. Banting FG, Best CH, Collip JB, Campbell WR, Fletcher AA. Pancreatic extracts in the treatment of diabetes mellitus. *Can Med Assoc J* 1922;12:141-6.
2. The diabetes control and complications trial research group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329:977-86.
3. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group [see comments]. *Lancet* 1998;352:837-53.
4. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643-53.
5. Mollema ED, Snoek FJ, Heine RJ, van der Ploeg HM. Phobia of self-injecting and self-testing in insulin-treated diabetes patients: opportunities for screening. *Diabet Med* 2001;18:671-4.
6. Zambanini A, Newson RB, Maisey M, Feher MD. Injection related anxiety in insulin-treated diabetes. *Diabetes Res Clin Pract* 1999;46:239-46.
7. Owens DR. New horizons – alternative routes for insulin therapy. *Nat Rev Drug Discov* 2002;1:529-40.
8. Laube BL. Treating diabetes with aerosolized insulin. *Chest* 2001;120:99S-106S.
9. Gaensslen M. Ueber inhalation von insulin. *Klin Wochenschr* 1925;2:71-2.
10. Wigley FW, Londono JH, Wood SH, Shipp JC, Waldman RH. Insulin across respiratory mucosae by aerosol delivery. *Diabetes* 1971;20:552-6.
11. Patton JS, Bukar J, Nagarajan S. Inhaled insulin. *Adv Drug Deliv Rev* 1999;35:235-47.
12. Schulz H. Mechanisms and factors affecting intrapulmonary particle deposition: implications for efficient inhalation therapies. *Pharmaceutical Science & Technology Today* 1998;1:336-44.
13. Himmelmann A, Jendle J, Mellen A, Petersen AH, Dahl UL, Wollmer P. The impact of smoking on inhaled insulin. *Diabetes Care* 2003;26:677-82.
14. Rave K, Bott S, Heinemann L, et al. Time-action profile of inhaled insulin in comparison with subcutaneously injected insulin lispro and regular human insulin. *Diabetes Care* 2005;28:1077-82.
15. Skyler JS, Cefalu WT, Kourides IA, et al. Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomised proof-of-concept study. *Lancet* 2001;357:331-5.
16. Quattrin T, Belanger A, Bohannon NJ, Schwartz SL. Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneous insulin therapy in patients with type 1 diabetes: results of a 6-month, randomized, comparative trial. *Diabetes Care* 2004;27:2622-7.

17. Skyler JS, Weinstock RS, Raskin P, et al. Use of inhaled insulin in a basal/bolus insulin regimen in type 1 diabetic subjects: a 6-month, randomized, comparative trial. *Diabetes Care* 2005;28:1630-5.
18. DeFronzo RA, Bergenstal RM, Cefalu WT, et al. Efficacy of inhaled insulin in patients with type 2 diabetes not controlled with diet and exercise: a 12-week, randomized, comparative trial. *Diabetes Care* 2005;28:1922-8.
19. Barnett AH. Efficacy and one-year pulmonary safety of inhaled insulin (Exubera) as adjunctive therapy with metformin or glibenclamide in type 2 diabetes patients poorly controlled on oral agent monotherapy. *Diabetes* 2004;53:A107.
20. Rosenstock J, Zinman B, Murphy LJ, et al. Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* 2005;143:549-58.
21. Cefalu WT, Skyler JS, Kourides IA, et al. Inhaled human insulin treatment in patients with type 2 diabetes mellitus. *Ann Intern Med* 2001;134:203-7.
22. Hollander PA, Blonde L, Rowe R, et al. Efficacy and safety of inhaled insulin (exubera) compared with subcutaneous insulin therapy in patients with type 2 diabetes: results of a 6-month, randomized, comparative trial. *Diabetes Care* 2004;27:2356-62.
23. Brunner GA, Balent B, Ellmerer M, et al. Dose-response relation of liquid aerosol inhaled insulin in type I diabetic patients. *Diabetologia* 2001;44:305-8.
24. McElduff A, Mather LE, Kam PC, Clauson P. Influence of acute upper respiratory tract infection on the absorption of inhaled insulin using the AERx insulin Diabetes Management System. *Br J Clin Pharmacol* 2005;59:546-51.
25. Hermansen K, Ronnema T, Petersen AH, Bellaire S, Adamson U. Intensive therapy with inhaled insulin via the AERx insulin diabetes management system. *Diabetes Care* 2004;27:162-7.
26. Rave KM, Nosek L, de la Pena A, et al. Dose response of inhaled dry-powder insulin and dose equivalence to subcutaneous insulin lispro. *Diabetes Care* 2005;28:2400-5.
27. Garg S, Rosenstock J, Silverman BL, et al. Efficacy and safety of preprandial human insulin inhalation powder versus injectable insulin in patients with type 1 diabetes. *Diabetologia* 2006;DOI 10.1007/s00125-006-0161-3.
28. Steiner S, Pfutzner A, Wilson BR, Harzer O, Heinemann L, Rave K. Technosphere/Insulin – proof of concept study with a new insulin formulation for pulmonary delivery. *Exp Clin Endocrinol Diabetes* 2002;110:17-21.
29. Perera AD, Kapitza C, Nosek L, et al. Absorption and metabolic effect of inhaled insulin: inpatient variability after inhalation via the Aerodose insulin inhaler in patients with type 2 diabetes. *Diabetes Care* 2002;25:2276-81.
30. Royle P, Waugh N, McAuley L, McIntyre L, Thomas S. Inhaled insulin in diabetes mellitus. *Cochrane Database Syst Rev* 2003;CD003890.
31. Asplin CM, Hollander PM, Palmer JP. How does glucose regulate the human pancreatic A cell in vivo? *Diabetologia* 1984;26:203-7.
32. Brain JD. Unlocking the opportunity of tight glycaemic control. Inhaled insulin: safety. *Diabetes Obes Metab* 2005;7(suppl 1):S14-8.
33. Dreyer M. Efficacy and two-year pulmonary safety of inhaled insulin as adjunctive therapy with metformin or glibenclamide in Type 2 diabetes patients poorly controlled with oral monotherapy. *Diabetologia* 2004;47:A44-5.
34. Skyler J. Sustained long-term efficacy and safety of inhaled insulin during 4 years of continuous therapy. *Diabetes* 2004;53:A115.
35. Ramirez LC, Dal NA, Hsia C, et al. Relationship between diabetes control and pulmonary function in insulin-dependent diabetes mellitus. *Am J Med* 1991;91:371-6.
36. Hsia CC, Raskin P. The diabetic lung: relevance of alveolar microangiopathy for the use of inhaled insulin. *Am J Med* 2005;118:205-11.
37. Fineberg SE, Kawabata T, Finco-Kent D, Liu C, Krasner A. Antibody response to inhaled insulin in patients with type 1 or type 2 diabetes. An analysis of initial phase II and III inhaled insulin (Exubera) trials and a two-year extension trial. *J Clin Endocrinol Metab* 2005;90:3287-94.
38. Freemantle N, Blonde L, Duhot D, et al. Availability of inhaled insulin promotes greater perceived acceptance of insulin therapy in patients with type 2 diabetes. *Diabetes Care* 2005;28:427-8.
39. Rosenstock J, Cappelleri JC, Bolinder B, Gerber RA. Patient satisfaction and glycemic control after 1 year with inhaled insulin (Exubera) in patients with type 1 or type 2 diabetes. *Diabetes Care* 2004;27:1318-23.
40. Gerber RA, Cappelleri JC, Kourides IA, Gelfand RA. Treatment satisfaction with inhaled insulin in patients with type 1 diabetes: a randomized controlled trial. *Diabetes Care* 2001;24:1556-9.
41. Cappelleri JC, Cefalu WT, Rosenstock J, Kourides IA, Gerber RA. Treatment satisfaction in type 2 diabetes: a comparison between an inhaled insulin regimen and a subcutaneous insulin regimen. *Clin Ther* 2002;24:552-64.
42. Freemantle N, Blonde L, Bolinder B, et al. Real-world trials to answer real-world questions. *Pharmacoeconomics* 2005;23:747-54.

If it works by inhalation,  
why not try it as shampoo?

