Editorial

Inhaled Insulin

The concept of inhaled insulin was initially investigated in 1924, but the first demonstration of its glucose-lowering effect in an animal model system occurred only in 1971. The presence of a large surface area (approximately 140 m$^2$) provides the physiological rationale for use of the respiratory tree for delivery of polypeptide drugs such as insulin. The alveoli are lined by very thin (0.1–0.2 µm), vesiculated and richly perfused epithelial cells, which are highly permeable and devoid of any enzymatic digestion. The key technological event for using this route for drug delivery is to ensure the dispersal of insulin particles, because large-sized particles will not reach the alveolar tree. The nature of aerosol particles is dependent on their mass median aerodynamic diameter (MMAD), which is a function of the geometric diameter and density of the particle. Particles with an MMAD of 1.5–2.5 µm are capable of deposition in the lung alveoli. In the alveoli, insulin particles are taken up in the vesicles, transported across the capillary membrane and released into the bloodstream. In addition to particle diameter, smoking, upper respiratory infection and asthmatic airway disease can also affect the delivery of insulin to the alveoli.

The ideal pulmonary device to deliver insulin should be portable, easy to use with minimal patient education, rechargeable, moisture proof and capable of emitting a constant dose to the lungs without being affected by the inhalation rate of the patient. There are three main projects involving inhaled insulin, namely Exubera (Nektar/Pfizer/Aventis), AERx (Aradigm/Novo Nordisk) and AIR (Alkermes/Eli Lilly). While dry insulin in the Exubera device is combined with mannitol, glycine and sodium citrate, that in AIR is combined with dipalmitoyl glycerol-phosphocholine, a normal component of alveolar surfactant. The AERx device delivers a fine particle liquid aerosol spray.

The bioavailability of inhaled insulin is approximately 10%–13% of subcutaneous insulin, which necessitates an 8–10-fold higher dose requirement using this delivery system. Studies have shown that the onset of action of inhaled insulin varies from 5 to 15 minutes. The peak action of inhaled insulin (45–60 minutes) is faster compared with regular insulin but similar to that observed with short acting analogues. The duration of action of inhaled insulin (4–6 hours) has been demonstrated to be longer than that of short acting insulin analogues (3–5 hours). This faster onset and longer duration of action of inhaled insulin makes it more suitable for postprandial glycaemic excursion coverage without causing late postprandial hypoglycaemia.

The acute effect of cigarette smoking includes mucosal irritation, reflex changes in muscle tone of the bronchial tree and increased vasoconstriction, thus decreasing peak flow, forced vital capacity (FVC), and forced expiratory volume (FEV$\text{\textsubscript{1}}$) and has an adverse effect on the regional distribution of blood flow. Recent studies show that while the maximum insulin concentration following inhaled insulin is significantly more in smokers compared with non-smokers, smokers are less sensitive to insulin than non-smokers irrespective of the route of administration. Hence, despite the increased peak insulin concentration seen in smokers, the glucodynamic effect is partially offset, most likely because of increased insulin
This effect on peak insulin concentration tends to normalize with cessation of smoking, while resumption of smoking completely reverses the effect of cessation of smoking. In view of the significant effect of cessation and resumption of smoking on the pharmacokinetics of inhaled insulin, it should not be used in people with diabetes who choose to continue smoking. This is consistent with the recommendation that people with diabetes should refrain from smoking altogether. However, ex-smokers can be considered for inhaled insulin use if their other pulmonary functions remain normal.

Individuals with an acute upper respiratory tract infection do not have any alteration in the pharmacokinetics of inhaled insulin. Hence, such individuals need neither discontinue therapy with inhaled insulin nor make any dose adjustments. There have been concerns about the long term potential impact of inhaled insulin on pulmonary function. However, in the majority of studies, pulmonary functions are not affected by inhaled insulin, though there is greater decrease in diffusion capacity for carbon monoxide.

Data from clinical trials suggest that inhaled insulin is quite safe. Cough of mild-to-moderate severity is the commonest side-effect, which decreases during treatment and neither disturbs the patient’s routine nor necessitates discontinuation of treatment. The overall incidence of hypoglycaemia appears to be more with inhaled insulin compared with injectable insulin. Relatively higher insulin-binding antibody titres are seen with inhaled insulin as compared with injectable insulin. However, this has not been shown to be associated with any adverse clinical consequences such as hypoglycaemia or erratic glycaemic control.

Trials of inhaled insulin have been conducted in patients with type 1 and type 2 diabetes mellitus. In two large studies involving more than 300 subjects with type 1 diabetes, inhaled insulin was compared with conventional regimens using injectable insulin. Mean glycosylated haemoglobin (HbA1c) decreased comparably in the two groups and a similar proportion of individuals attained target HbA1c values. However, treatment satisfaction was significantly more in patients on inhaled insulin. Overall satisfaction with inhaled insulin was also reported to be significantly more (35.1% v. 10.6%) by Gerber et al. The intra-subject variability was reported to be comparable between patients receiving inhaled insulin and subcutaneous insulin, thereby confirming the reproducibility of this route of delivery. Data from these studies suggest that inhaled insulin provides glycaemic control comparable to that with a conventional insulin regimen and provides greater overall patient satisfaction than subcutaneous insulin.

In subjects with type 2 diabetes, inhaled insulin has either been compared with regimens involving oral hypoglycaemic agents (OHAs) or with conventional insulin therapy in subjects with secondary OHA failure. Rosenstock et al. in an open label, randomized controlled trial compared inhaled insulin alone, inhaled insulin and OHA combination, and OHA alone for 12 weeks and found that inhaled insulin improved glycaemic control and HbA1c when added to or substituted with OHA. In subjects with suboptimal control on diet and exercise, pre-meal inhaled insulin resulted in better glycaemic control compared with rosiglitazone. In patients with secondary OHA failure, inhaled insulin and a bedtime dose of ultralente insulin resulted in similar glycaemic control compared with regimens using twice daily subcutaneous pre-mixed insulin. The proportion of patients reaching a target HbA1c of <7% was more in the inhaled insulin group. In another study, inhaled insulin immediately before meals was compared with subcutaneous fast-acting human insulin administered 30 minutes before meals, both in combination with evening NPH insulin. While no significant difference was observed in HbA1c, fasting serum glucose was significantly lower in the inhaled insulin group compared with the subcutaneous group. In a trial involving patients with inadequate control despite therapy with a sulphonylurea and/or metformin, the addition of inhaled insulin resulted in significantly greater reduction in HbA1c. These studies suggest that in patients with type 2 diabetes, inhaled insulin improves glycaemic control.
when added to ongoing OHA therapy and provides glycaemic control comparable with the conventional subcutaneous insulin regimen.

Some important questions remain unanswered, which will influence the eventual place of inhaled insulin in the therapeutic options for people with diabetes. These include long term efficacy, tolerance and pulmonary safety, impact of immunogenicity, use in patients with respiratory disease and long term acceptability, especially in patients with type 2 diabetes. The cost of therapy, which at present is considerably more than that of injectable insulin, together with practical issues related to inhalation devices will also have an effect on therapy with inhaled insulin. In view of these pending issues, the National Institute for Health and Clinical Excellence (NICE) in the UK does not yet recommend inhaled insulin for therapy of patients with diabetes except in the context of clinical studies. NICE is also in the process of performing a cost–benefit analysis of this therapy to help reach a recommendation on its use in routine clinical practice.

In conclusion, inhaled intrapulmonary insulin offers an attractive and viable alternative to subcutaneous injections for delivery of insulin in people with diabetes. Inhaled insulin has faster onset of action and therefore can be taken just prior to a meal. The relative bioavailability of inhaled insulin is lower than that of subcutaneous insulin, which leads to an increase in dose requirements by 8–10-fold. Therapy with inhaled insulin can cause a mild-to-moderate cough, which usually does not interfere with the patient’s routine activities. In both patients with type 1 and type 2 diabetes, treatment with inhaled and injectable insulin results in comparable glycaemic control, though with significantly greater patient satisfaction in those receiving inhaled insulin. There remain some unanswered questions regarding long term use, convenience and cost–benefit ratio of inhaled insulin which will guide future recommendations for its use in the standard medical care of patients with diabetes.

REFERENCES
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