

Inhaled insulin: where are we and where might we go?

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Inhalation is an attractive alternative to injection, but significant issues will limit its use

Insulin is an excellent therapeutic agent with few significant side effects, apart from hypoglycaemia. However, it has one major disadvantage — it needs to be given by injection. Patients' fears or reservations often mean doctors are reluctant to initiate insulin therapy, even when it is clearly indicated.

Not surprisingly, many attempts have been made to find an alternate method of insulin delivery, through nasal, oral, buccal, transdermal or inhaled routes. Inhaled insulin is a theoretically attractive approach, mainly because of the large absorptive surface of the lung alveoli with relatively little proteolytic activity to cause insulin degradation, and it is the most advanced alternative method for insulin delivery in development. One such product, Exubera (Pfizer), has already been granted approval for clinical use in the United States and the European Union, and other products (AERx [Novo Nordisk] and AIR [Eli Lilly]) are in advanced stages of clinical trials.

The technology required for administering inhaled insulin is more exacting than that for other inhalation medications, such as those used in treating asthma. As the dose–response curve to insulin is a near linear one, it is critical that the right amount of insulin be consistently delivered to the alveoli and blood stream. The size of the inhaled insulin particles is of paramount importance to this, as particles that are too large adhere to the upper airway and are not absorbed, while those too small will be exhaled before absorption. Manufacturers have used different technologies to address this, and clinical studies have shown that variability of inhaled insulin absorption is similar to that for subcutaneous insulin.¹

Pharmacokinetic studies have shown inhaled insulin to be similar to the rapid-onset insulin analogues, such as insulin lispro or insulin aspart, but with a slightly longer duration of action. In other words, inhaled insulin is essentially a rapid-acting insulin suitable for control of postprandial hyperglycaemia. More recent clinical studies suggest that inhaled insulin also slightly lowers fasting plasma glucose levels,² but the clinical significance of this finding has yet to be fully explored. Inhaled insulin has so far been used in combination with injections of long-acting insulin, and this practice will continue, particularly for patients with type 1 diabetes. In this context, inhaled insulin has been shown to be equivalent to subcutaneous insulin in the control of hyperglycaemia in a number of relatively long-term trials (1–2 years) encompassing all major clinical scenarios encountered in type 1 or type 2 diabetes. However, no clinical trials have shown that inhaled insulin is superior to conventional insulin administration in metabolic control.

Clinical trials and theoretical considerations have raised a few potential problems with inhaled insulin, including:³

- Insulin delivered via the lungs is more antigenic and results in increased development of anti-insulin antibodies, a problem largely eliminated from conventional insulin treatment by the use of purified insulin. However, these antibodies have not been found to cause major problems, such as allergy reactions or insulin resistance, and they are also unlikely to play a dominant role in the evolution of diabetic complications.

- Long-term delivery of a foreign substance to the respiratory tract can potentially cause damage. There is little doubt that treatment with inhaled insulin is associated with a small (about 5%) decline in lung function, when measured by parameters such as the diffusing capacity of the lung for carbon monoxide, and forced expiratory volume in 1 second.³ Fortunately, it appears that this relatively minor decline is reversible when inhaled insulin treatment is suspended.⁴

- There is a theoretical increased risk of formation or promotion of cancer with chronic use, especially since insulin is a relatively potent growth factor. This potential danger has not eventuated after use of inhaled insulin in thousands of patients, however it is prudent to carefully monitor for this possible side effect.

There are also practical issues with use of inhaled insulin. Smoking immediately before inhalation of insulin increases insulin absorption, although passive or chronic smoking, asthma, and chronic airways disease decrease absorption.^{4–6} Inhaled insulin therapy is not associated with increased respiratory tract infection but often causes a mild, usually transient cough. Upper respiratory tract infections have shown no significant effect on insulin absorption in clinical trials, but tangible experience is relatively limited. These confounders of insulin absorption have been carefully avoided or controlled in clinical trials, but their potential to cause hypoglycaemia or hyperglycaemia in real-world use is obvious.

Some problems with inhaled insulin are highlighted by the commercially available Exubera. Due to its formulation and method of delivery, the dosage of Exubera needs to be measured in milligrams rather than the customary units. It is available in capsules of 1 mg (equal to 3 units) or 3 mg (equal to 8 units), and the product information recommends a commencing dosage based on the patient's body weight rather than the carbohydrate content of meals. To make things even more confusing, as noted above, three 1 mg capsules are more potent than one 3 mg capsule, complicating interchange of capsules of different strengths. These limitations make minor adjustments in insulin dosage more difficult, especially in patients with labile type 1 diabetes who can develop severe hypoglycaemia with insulin dose adjustment of as little as one or two units at a time. For patients with type 2 diabetes with a high insulin requirement, multiple (more time-consuming) inhalations are needed.

Most of the devices used to administer inhaled insulin are relatively large and cumbersome, and they require both time and skill to master. These factors will limit their uptake. In times past, routine tasks in the diabetic clinic included checking the glass syringe, usually carried in an alcohol solution in a special container, and inspecting the needle for sharpness. There has been an obvious improvement in the devices used to inject insulin subcutaneously, and it would be unfortunate if this trend were reversed with the use of inhaled insulin.

All these practical issues with inhaled insulin will probably be overcome in time, but at the moment they remain significant. In addition, absorption of inhaled insulin is not as efficient as subcutaneous injection. Indeed, only about 10% of the dose is

absorbed. This poor absorption and the high cost of development will inevitably make inhaled insulins much more expensive than their subcutaneous counterparts. This is almost certain to limit their use, particularly in Australia where government subsidy of a new pharmaceutical product largely depends on demonstration of its cost-effectiveness in comparison with existing alternative products. Although qualitative surveys have shown that patients given the choice of inhaled or injected insulin overwhelmingly prefer the former,^{4,7,8} this has not been shown to translate to wider or earlier acceptance of insulin treatment or a consequent lower glycated haemoglobin level for the diabetic community. The need for caution in the use of inhaled insulin in young patients and the relative lack of flexibility in adjusting dosage by a small amount make it more likely to be used as the initial insulin therapy for patients with type 2 rather than type 1 diabetes. However, for most doctors, who all too often see patients refuse insulin injections when they are needed, the availability of inhaled insulin will be a step forward, at least for some of their patients.

In summary, we predict that inhaled insulin therapy will become part of our therapeutic armamentarium, albeit with a small niche market. A small proportion of patients with well controlled type 1 diabetes may use the inhaled route exclusively. Others may use inhaled insulin as a supplement, or to have a much needed "injection holiday". Subcutaneously injected insulin will remain the major route of administration for the foreseeable future. The inhaled insulins currently available will primarily be used by adult patients with type 2 diabetes who have the financial means — and who are willing to pay — to avoid injections. We suggest that the regulatory authorities could make inhaled insulin available to individual patients for a limited time through the Pharmaceutical Benefits Scheme, to allow patients and their doctors to trial inhaled insulin therapy and assess its benefits.

Competing interests

Aidan McElduff has performed clinical trials on inhaled insulin for Novo Nordisk, and has received support from Eli Lilly and Novo Nordisk to attend meetings. Dennis Yue has performed clinical trials on inhaled insulin for Pfizer, and staff in his department have performed clinical trials for Novo Nordisk. He is also on the Global Advisory Panel of Pfizer for inhaled insulin, and has received support from Eli Lilly, Novo Nordisk, and Pfizer to attend meetings.

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