

Inhaled insulin

Added to oral agents, it may eventually replace injections

In January 2006 the US Food and Drug Administration approved the first inhalable insulin preparation for treatment of types 1 and 2 diabetes mellitus. This preparation, marketed by Pfizer, is a dry, powdered, human, regular insulin that is made into an aerosol mechanically by a handheld device at the time of inhalation. The powder is prepackaged in 1 mg foil packets that deliver 3 units of insulin and 3 mg packets that deliver 9 units. Because one unit of subcutaneous insulin corresponds to about 30 µg insulin, the activity of inhaled insulin is only about 10% of injected insulin on a weight basis.

This "inefficiency" in comparison to subcutaneous insulin brings up the reproducibility of dosing. Firstly, in clinical trials the overall incidence of hypoglycaemia seems comparable with inhaled and subcutaneous insulin when comparable levels of glycaemic control are obtained. However, severe hypoglycaemia was more common and mild hypoglycaemia less common with the inhaled product in some trials. This will bear watching in longer term follow-up studies. Secondly, pulmonary factors (specifically smoking status and asthma) affect the absorption of inhaled insulin, with increased absorption in smokers and decreased absorption with asthma. Therefore, populations in whom the variability of absorption is greatest (current and recent smokers) are not considered appropriate candidates for inhaled insulin therapy.

Inhaled insulin is rapid acting, with a peak plasma exposure between 30 and 90 minutes after dosage (similar to rapid acting insulin analogues). However, inhaled insulin taken before a meal has been observed to have a more marked effect on fasting glycaemia in humans than pre-meal subcutaneous insulin,¹ suggesting a prolonged action. Also, in animal studies, inhaled insulin seems to have a lesser effect on hepatic glucose production, with a correspondingly greater effect on peripheral glucose disposal, than intravenously infused regular insulin.² Whether this will apply to humans is not known.

Considering efficacy, phase 3 trials are reasonably convincing that overall glycaemic control as assessed by haemoglobin A_{1c} is similar with pre-meal subcutaneous regular insulin and the inhaled product in patients with type 1 diabetes or type 2 diabetes. In patients with type 1 diabetes, preprandial inhaled insulin has been studied in combination with insulin glargine, bedtime ultralente,³ and twice daily isophane insulin (NPH).⁴ Efficacy in patients with type 2 diabetes has been assessed in patients suboptimally controlled

by diet and exercise randomised to maximal dose rosiglitazone versus pre-meal inhaled insulin⁵ as well as those receiving stable basal or bolus insulin treatment.⁶ The effect of pre-meal inhaled insulin when added to an existing oral regimen was studied in a phase 2 trial of patients in whom oral treatment with sulfonylurea or metformin had failed.⁷

For type 1 diabetes, inhaled insulin is likely to be accepted by both the public and the medical community. It is perhaps surprising how frequently individuals with longstanding type 1 diabetes, who seem to have adapted to multiple daily injections, are excited by the potential of needing only a single, long acting insulin injection daily, with inhaled insulin replacing pre-meal injections.

The market for inhaled insulin in type 2 diabetes is more complex. Inhaled insulin has been under development for a number of years. Thus it will enter a very different therapeutic landscape for type 2 diabetes than was evident at the time of its initial study. In addition to the newer thiazolidinediones, the recent introduction of both exenatide (Byetta) and pramlintide (Symlin) and the likely imminent introduction of the dipeptidyl peptidase-4 (DPP-4) inhibitors allow additional therapeutic combinations with established oral hypoglycaemic agents. Why then consider insulin? One reason relates to potency. Insulin, regardless of route of administration, remains our most potent glucose lowering therapy. A second reason may be safety. Insulin has been used for 80 years and its side effects are well known; therefore, inhaled insulin has the potential to be beneficial in the long term too. The effect of treating hyperglycaemia for even four or five years with DPP-4 inhibitors or exenatide is unknown.

But do we know all the risks of inhaled insulin, or does the route of insulin delivery affect the risk of adverse events? Approval was delayed substantially so that the clinical importance of increases of anti-insulin antibody production and small decreases in lung function seen during phase 3 trials could be evaluated.⁸⁻⁹ Current evidence indicates that these adverse findings are not clinically worrisome, although longer term monitoring is planned.

Other potential barriers to acceptance of inhaled insulin include cost and patient satisfaction. The cost of inhaled insulin and the accompanying delivery device is not set, but it will certainly substantially exceed that of injectable insulin. Regarding patient satisfaction, perception of tolerability of the regimen and ease of use were significantly greater in patients randomised to

inhaled insulin, and a large proportion of patients randomised to inhaled insulin chose to continue with that regimen. These findings held regardless of type of diabetes or whether inhaled insulin was added to subcutaneous insulin therapy or oral agents.¹⁰⁻¹²

Given the comparable glycaemic control and safety profile seen with the inhaled insulin preparation in comparison to subcutaneous administration, patient acceptance may prove to be the primary determinant of marketplace success. For some patients, doctors and budget holders, the issue of drug costs, cost effectiveness, and uncertainty regarding potential long term adverse effects related to pulmonary route of delivery will outweigh the perceived benefits of ease of administration.

Both considerations contributed to the recent decision by NICE (the National Institute for Health and Clinical Excellence) to decline funding for inhaled insulin for the NHS. This opinion will be revisited after several months of public commentary.¹³ However, patients with type 1 diabetes or insulin dependent type 2 diabetes who are distressed by frequent injections may be able to improve their blood sugar control substantially and avoid complications from diabetes with this new product. For patients with type 2 diabetes with failing oral agents who are reluctant to start treatment with insulin, inhaled insulin offers the same efficacy as subcutaneous insulin, without multiple daily injections. When added to oral agents, it may obviate the need for subcutaneous insulin entirely.

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Passive smoking's role in diabetes

More evidence of the harmfulness of tobacco smoke

Smoking is the main cause of lung cancer, chronic obstructive pulmonary disease, and peripheral atherosclerosis and one of the most important risk factors for cardiovascular disease. In particular, the risk attributed to current smoking varies from 40% for coronary heart disease to more than 60% for cancers of the pharynx and oesophagus and more than 80% for lung cancer.¹ In addition, the exposure of non-smokers to environmental tobacco smoke has been associated with a substantial increase in their risk of coronary heart disease and cancer.^{2,3} Several investigators have suggested that both active and passive smoking affects the cardiovascular system through endothelial dysfunction, increases in oxidised low density lipoprotein cholesterol, platelet adherence, inflammation, and mitochondrial and oxidative damage, as well as an acute deterioration in the elastic properties of the aorta.⁴⁻⁷ Indeed, some of the effects of passive smoke on the cardiovascular systems of non-smokers are comparable to the effects of smoking on smokers.³ Now comes another effect of active and

passive smoking: an increased risk of glucose intolerance.

In this issue (p 1064) Houston et al show an increased risk from tobacco smoke of glucose intolerance,⁸ which is a precursor of diabetes and atherosclerotic disease.⁹ In particular, they found a strong association between exposure to tobacco smoke and the incidence of glucose intolerance during the 15 year follow-up of young adults. The incidence of glucose intolerance was 22% among smokers, 17% among those who never smoked but had been exposed to smoke, 14% among former smokers, and 12% among those who had never smoked and had no passive smoke exposure. In addition, the authors reported that current and never smokers with passive smoke exposure experienced, respectively, 65% and 35% higher risks of developing glucose intolerance than never smokers without passive exposure, even after adjustment for various baseline sociodemographic, biological, and behavioural factors. Moreover, in the analyses stratified by race and sex the risks of glucose

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