REVIEW

Inhaled insulins

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As a result of knowledge gained from the management of asthma with inhalers and nebulisers, pulmonary delivery devices for insulin have been developed. Particle size of the aerosol particularly influences drug delivery. Although several pharmaceutical companies are developing different systems, Pfizer have launched the first inhaled insulin (Exubera). Clinical trials have taken place in patients with both type 1 and type 2 diabetes, but have shown similar glucose control as subcutaneous insulin delivery. However, patient satisfaction does seem to be increased in patients taking inhaled insulins. Further studies are needed to investigate compliance, side-effect profiles, quality of life, long-term glycaemia control and cost effectiveness.

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Insulin was first discovered in 1923. It was originally given intramuscularly, but this was associated with abscess formation. It was soon shown that subcutaneous delivery of insulin was just as effective.

As the prevalence of type 1 diabetes and particularly type 2 diabetes increases, the demand for insulin has increased, and alternative routes of delivery have been tried, including dermal, oral, buccal, nasal, rectal, vaginal and of course pulmonary.[1–3] With the exception of the pulmonary route, all have major disadvantages, particularly the oral route, which exposes insulin to certain peptidases and first pass metabolism.

The recent guidelines re-emphasise the need for stricter control of blood glucose in patients with diabetes. A significant proportion of patients fail to reach targets with oral hypoglycaemic agents alone and warrant insulin treatment.[4 5]

Early days

Pulmonary delivery of insulin was first reported as an alternative to injection in 1925.[6] In this early report, it was stated that insulin given as an aerosol could produce a decrease in blood glucose levels.

In the 1970s, Wigley *et al*[7] showed hypoglycaemic effects of insulin delivered as an aerosol using a nebuliser in rabbits. They then went on to show that there was an increase in plasma levels of immunoreactive insulin in three subjects without diabetes and in four subjects with diabetes, and that hypoglycaemia showed a temporal relationship with plasma levels of insulin. It was not until 2000 that the modern era of inhaled insulin began.

Pulmonary drug delivery

The knowledge gained from management of asthma with inhalers and nebulisers and dry powder inhalers have facilitated the development of pulmonary delivery systems for insulin. The lung provides an excellent route of administration because of its large surface area (between 50 and 140 m^2) for systemic absorption.

The alveolar–capillary barrier enables rapid absorption of large insulin molecules, possibly by transcytosis and paracellular mechanisms and, therefore, a rapid onset of action after inhalation.[8] After inhalation, a relatively small amount of the dose inhaled is available for absorption (10–15%), but given a sufficient inhaled dose, this is clinically effective.[9 10] Inhaled insulin has an onset of action faster than soluble insulin and similar to that of an analogue after subcutaneous injection (15–40 min).[11–13] Studies have shown a duration of action of about 6 h with inhaled insulin, which is longer than that of subcutaneous lispro insulin but somewhat comparable to subcutaneous regular insulin.[14 15]

Factors altering pulmonary delivery of insulin

A major challenge with pulmonary drug delivery is the lack of reproducibility in the deposition site of the administered dose.[16] Many factors influence the deposition of drug within the respiratory tract—namely, the mode of inhalation and aerosol properties. In addition, the type of propellant used, losses within the device, volume inhaled, the flow rate and breath-holding pauses influence drug delivery.

The particle size of the aerosol also influences drug delivery. The ideal size for pulmonary delivery is between 1 and 5 μm assuming that the density of the particle is 1 g/cm^3.[17]

Delivery systems

Several pharmaceutical companies are developing different pulmonary insulin delivery systems. The delivery system greatly influences the clinical efficacy. All delivery systems are used to deliver regular insulin, either in powder form or in solution. The powder is present in amorphous form and hence is more stable during storage. However, the insulin formulation is irrelevant if the delivery device does not generate an appropriate aerosol.[2]

The Exubera system developed by Nektar Therapeutics (San Carlos, California, USA) has been used by Pfizer. It is the most widely studied pulmonary insulin delivery system and will soon be available for clinical use in the UK, Germany, Ireland and USA. Phase III clinical trials have been

Abbreviations: FEV_1, forced expiratory volume in 1 s; HbA_{1c}, haemoglobulin A 1c; NICE, National Institute of Clinical Excellence

completed, and its use has been approved by the FDA in 2006.[10 18–20]

The Exubera inhaler generates a pulse of compressed air and thus deagglomerates the dry power into an aerosol. The bioavailabity of insulin is about 10% compared with regular insulin given by subcutaneous injection.[21] The inhaled insulin should be administered 10 min before the start of a meal. The inhaled insulin device is relatively bulky and involves a fivestep procedure for every blister of insulin required. The mechanism for delivery of the prepackaged insulin could be considered by some to be complex and the delivery of relatively small doses of insulin more time consuming.[22]

CLINICAL EFFICACY

The following discussion is based on the results of clinical trials with Exubera, as results with other inhaled insulin systems have not yet been published.

Type 1 diabetes

There have been three major clinical trials in patients with type 1 diabetes comparing inhaled insulin with subcutaneous insulin.[23–25]

The studies were not blinded (as that would be unethical), and none of the studies used a long acting insulin analogue glargine nor regimens using short acting insulin analogues. In most of the studies undertaken, the patient characteristics are poorly described, with a lot of exclusion criteria. The results may therefore be difficult to generalise. However, the studies show an improvement in the haemoglobulin A 1c (HbA_{1c}) level and clinical efficacy seemed to be comparable to that of subcutaneously injected insulin.[25]

Type 2 diabetes

Inhaled insulin has been used in a number of trials in patients with type 2 diabetes. Three trials have studied patients who failed to reach glycaemic goals while taking conventional oral drug treatment.[26–28] A recently published study has shown the superiority of inhaled insulin over metaformin as an add-on treatment in patients with type 2 diabetes who failed to achieve glycaemic goals while taking sulphonylureas.[29 30] In one study, the efficacy of inhaled insulin in patients with suboptimal glycaemic control on diet and exercise, was compared with the efficacy of rosiglitazone. In this 12-week trial, inhaled insulin was shown to be as effective.[31]

PATIENT SATISFACTION, ACCEPTANCE AND COMPLIANCE

Patient satisfaction has been measured using the Patient Satisfaction with Insulin Therapy (PSIT) questionnaire, which looked at attributes of satisfaction, both with inhaled and injected insulin therapy.[32]

All trials showed significantly greater satisfaction with inhaled insulin, perhaps because of reduced number of daily injections.[33] In addition, switching from inhaled insulin to subcutaneously injectable insulin showed a trend towards deteriorating satisfaction.[34]

Studies have shown that availability of inhaled insulin has a greater acceptance of insulin therapy in patients with uncontrolled type 2 diabetes. Therefore, initiation of insulin therapy may be easier at an earlier stage in those with poorly controlled type 2 diabetes.[35]

HYPOGLYCAEMIC EPISODES

All the trials compared inhaled insulin with soluble but not short acting analogues. Theoretically, the risks of hypoglycaemia with inhaled insulin should be similar to subcutaneously injected short acting analogues as their absorption profiles are similar. There was variability between hypoglycaemic events with inhaled insulin as compared with subcutaneous insulin when comparable levels of glycaemic control were achieved.[19 36] Some studies showed that there was a higher risk of severe hypoglycaemic events with inhaled insulin than with subcutaneous insulin, but other studies showed either slightly less or slightly greater risk of mild hypoglycaemic events.[20 24]

However, studies have shown that the risk of hypoglycaemia is higher with inhaled insulin (Exubera) than with oral hypoglycaemic therapy, which is consistent with efforts to achieve better glycaemic control.[27 28 37] The risks of hypoglycaemia were comparable to that of subcutaneous insulin.[24 26]

This potential risk of developing insulin-induced hypoglycaemia should be part of the ''educational package'' just as it is in the case of the initiation of subcutaneous insulin.

INSULIN ANTIBODIES

Insulin antibody formation was reported to be increased with inhaled insulin as a result of immunological sensitivity of the pulmonary system.[38] There is concern that it might have effects on the action of insulin and that there might be release of insulin in an unpredictable manner from the circulating insulin–antibody complexes, causing hypoglycaemia. However, trials to date do not yet indicate any significant clinical effect of these antibodies, but longer-term studies need to be undertaken.[39 40]

WEIGHT CHANGE

Most of the studies in subjects with type 1 diabetes showed little, if at all any, difference in weight changes between those taking inhaled insulin as compared with those taking subcutaneous insulin. One of the studies in subjects with type 2 diabetes showed significantly less gain in weight with inhaled insulin than with subcutaneous insulin. However, this was not the case in another study.[20]

In patients with type 2 diabetes, inhaled insulin was shown to produce greater weight gain than oral hypoglycaemic agents.[41]

PULMONARY CONCERNS

Pulmonary function test, including forced expiratory volume in 1 s (FEV_1), forced vital capacity, total lung capacity and carbon monoxide diffusing capacity have been measured in studies on inhaled insulin. Some studies have indicated that the carbon monoxide diffusing capacity is reduced following inhaled insulin treatment.[42] The significance of the change is not yet known.

The alveolar–capillary network receives the entire cardiac output, making it the largest microvascular organ in the body and is therefore susceptible to microangiopathy. Owing to its large reserve, symptoms and disabilities of the lung are difficult to detect despite involvement. There is reduction in the elasticity of the lung, and there is some reduction in the forced vital capacity and FEV_1. Vascular changes are similar to those in kidney. Therefore, it is understandable that there are concerns about possible long-term effects of inhaled insulin on the pulmonary function tests in a patient with diabetes.

At present, it is recommended that all patients should undergo lung function tests, and there are clear criteria with regard to reduction in FEV_1 for discontinuation of inhaled insulin.[22]

The pulmonary changes are said to occur early after treatment initiation and are usually non-progressive, most resolving within 6 weeks of treatment discontinuation.[43]

Trials indicate greater incidence of cough in those using inhaled insulin, but this tends to decrease in incidence and prevalence over time.[18 19] The bioavailability is reduced and is contraindicated in those with asthma and severe (stage III or

stage IV) chronic obstructive pulmonary disease.[44] Smoking has been shown to increase the bioavailability of inhaled insulin. Because of the risks of hypoglycaemia, the use of inhaled insulin is currently contraindicated in smokers, even those who smoke occasionally and those who have smoked in the past 6 months. Those who resume smoking should immediately discontinue inhaled insulin.[45]

LIPOHYPERTROPHY AND INHALED INSULIN

It has been suggested that inhaled insulin might be an option for those who develop lipohypertrophy with subcutaneous insulin injections.[46] It has been shown in children and young adults with type 1 diabetes taking subcutaneous insulin that insulin antibody titres correlate with the degree of lipohypertrophy.[47] However, there are adipocytes in the lung as well and, at present, it is not known what effect inhaled insulin has on these cells.

COSTS/COST EFFECTIVENESS

A number of issues need to be considered when analysing the cost effectiveness of inhaled insulin. Clinical trials have shown that inhaled insulin is as efficacious as subcutaneous insulin when used in conjunction with basal insulins in patients with type 1 diabetes. Some patients preferred inhaled insulin possibly because of a reduction in the number of subcutaneous injections. As discussed earlier, more trials need to be undertaken using inhaled insulin along with long acting insulin analogues such as glargine and detemir plus, and short acting insulin analogues including lispro and aspart.

In patients with type 2 diabetes, the General Medical Services contract has put pressure for earlier initiation of insulin therapy particularly in patients who have ''failed'' on oral hypoglycaemic agents with HbA_{1c}>7.4%. A recent study has shown that in patients with type 2 diabetes, inhaled insulin therapy was better accepted than subcutaneous insulin (35% vs 15%).[48]

The second issue that would need to be looked into while performing an analysis is the perceived benefits in terms of improvement of quality of life.

The third issue would be to look at whether the compliance improves with inhaled insulin as compared with insulin injections.

There are no published cost-effectiveness studies on inhaled insulin. The manufacturers have submitted a cost–utility analysis to the National Institute of Clinical Excellence (NICE), based on a probabilistic Monte Carlo simulation model. Only patients with uncontrolled diabetes (HbA_{1c} >7.4% were considered in the model, and it was assumed that 35% of people with poorly controlled diabetes in the inhaled insulin arm would start inhaled insulin immediately, and the rest would start inhaled insulin 4 years later, whereas in the subcutaneous insulin arm only 15% would start insulin immediately. The compliance was assumed to be 100% and it was assumed that inhaled insulin achieved the same level of blood glucose control as the subcutaneous basal bolus regimen.[49] The cost of Exubera is based on the assumption that patients would need 0.15 mg of insulin per kilogram of body weight per day (at a unit cost of £0.2322 per mg—ie, £1102 for a dosage of 13 per day over a year). The average weight is assumed to be 76.54 kg for those with type 1 diabetes and 83.69 kg for those with type 2 diabetes. Therefore, inhaled insulin therapy would be estimated to cost an additional £500 per person per year.

The manufacturers have suggested that the utility of inhaled insulin was based on two things. First, the greater and earlier acceptance of insulin and, second, an assumption of an increase in health-related quality of life from taking inhaled insulin rather than an injection.

NICE believes that there is no evidence strong enough to suggest that patients might move on to inhaled insulin earlier and therefore avoid or delay long-term diabetic complications, and that inhaled insulin might not fully alleviate any problems relating to fears of injections, as individuals would still need to use needles for glucose testing. NICE states that at this point of time evidence is ''insufficient to provide support for a cost-effective use of this technology''.

In individuals with poor control, it is of key importance to identify the reasons for poor control, most of which may not be related to the insulin delivery system they use.

Even with perfect compliance, many patients do not achieve good glycaemic control with current insulin treatment and inhaled insulin should be no different. Therefore, when analysing added benefits for early initiation and better compliance, we have to consider these aspects of treatment before jumping to conclusions.

The other concern for effectiveness would be how effectively patients use the inhalers, because we know that even with proper self-management training a lot of people using inhalers for asthma do not use them as recommended.

In addition to the cost of the insulin in itself, we have to take into consideration the additional cost of equipment and also the need to train healthcare professionals, so that they can teach patients to use the inhalers.

OTHER ISSUES

Inhaled insulin would be of help to those with true needle phobia. It is estimated that there is some degree of needle phobia in at least 10% of the population.[50] But one has to remember that while taking inhaled insulin therapy the patient would have to continue checking his blood at home, similar to someone taking subcutaneous insulin therapy. In addition, it is perhaps more painful to check blood glucose at home than it is to take a subcutaneous injection with the newer pen devices. Therefore, needles cannot be avoided all together even if a patient is taking inhaled insulin. However, NICE states that inhaled insulin is a treatment option for anyone with a marked and persistent fear of injection (that meets Diagnostic and Statistical Manual of Mental Disorders -IV criteria for specific phobia ''blood injection injury type'').[49]

Other concerns regarding effectiveness must be considered, including correct usage of the inhaler. We are aware that many patients with asthma do not self-manage despite extensive inhaler training.[51] We also need to take into consideration the additional cost of the equipment, and the cost of training healthcare professionals to advise on the correct usage of inhaled insulin.

CONCLUSIONS

Inhaled insulin seems to be the first clinically effective alternative to subcutaneous insulin. It seems effective and safe in short-term studies. Further data are required, particularly in relation to its use with short acting and long acting analogues. In addition, long-term data are required on its use in those with diseased lungs and in smokers.

The earlier use of insulin in type 2 diabetes has been proposed so as to improve glycaemic control and delay the development of complications. If inhaled insulin is accepted more easily than subcutaneous insulin, it may be easier to initiate insulin therapy earlier in type 2 diabetes.

Further studies also need to be undertaken to look at compliance, side-effect profiles, quality of life, long-term glycaemic control and cost effectiveness.

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