Inhaled insulin: the solution for suboptimal diabetes control?

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For nearly a century, we have been using insulin to treat diabetes. Until recently, that insulin has been given by injection. In 2006, the first inhaled insulin, Exubera®, was licenced for use in Europe. The manufacturers hoped for a warm welcome – the end of injections and the dawn of a new era of enthusiastic insulin takers with perfect diabetic control. The National Institute for Health and Clinical Excellence (NICE) was more cautious and recommend that inhaled insulin only be used in the presence of diagnosed needle phobia (or severe intractable problems with injection sites) and should be supervised by diabetes specialists.[1] True needle phobia is rare and treatable by standard psychological techniques.[2,3] On the NICE criteria, the market for inhaled insulin may be small indeed.

Yet more and more people are taking – or being advised to take – more and more insulin. In type 1 diabetes, the numbers of administrations recommended per day has risen, with regimens designed to provide background insulinisation, independently of short- or rapid-acting insulins for meals.[4,5] In type 2 diabetes, it is rather the number of people considered eligible for insulin therapy that has increased. The strength of evidence showing the ability of strict glycaemic control to reduce risk of diabetic complications;[6] the degree of control required to limit large vessel damage;[7,8] and the progressive loss of insulin secretory capacity over time,[9] has lowered the threshold for defining 'failure' of treatment with lifestyle and oral antidiabetic agents alone. Insulin is being recommended to type 2 diabetic patients much earlier in the course of their disease. Yet we continue to delay starting insulin and compromise control by limiting the number of daily insulin administrations. If this is just because insulin is an injectable, Exubera® and its followers have the capacity to revolutionise the care of diabetes.

Insulin without injection

Exubera® offers patients the opportunity to introduce meal-time insulin without starting injections. It is not indicated in patients requiring only background insulin replacement to control fasting glycaemia. It is a fast-acting insulin, with a duration of action comparable to human soluble (regular) insulin rather than fast-acting analogues.[10] In trials, Exubera® is only 'non-inferior' to conventional (not analogue) insulins, the latter not always used in equivalent basal-bolus regimens[11–14] and in type 2, slightly more effective than adding a second oral agent in very poorly controlled disease.[15,16] It has not been tested against fully flexible analogue regimens. It is clear that inhaled insulin's sole advantage over injected insulin is its route of delivery.

Exubera® has low bioavailability, minor and probably reversible effects on lung function[17] and a natural lack of long-term safety data. Active smoking contraindicates its use because of increased bioavailabilty of inhaled insulin,[18,19] while absorption may be retarded in non-smokers exposed to smoke.[20] In patients with type 1 diabetes, there may be problems of dose flexibility: in the present formulation, the minimum unit for dose change is 1 mg, equivalent to 3 units of injected insulin (the 3 mg blister being equivalent to around 8 units). Type 1 patients also have a greater tendency to make insulin-binding antibodies with inhaled insulin.[21] Although this is reported not to affect efficacy or hypoglycaemia rate in the short- and medium-term,[22] those of us with memories of the days of 'dirty' insulins will recall the unpredictable absorption of insulin attributed to high levels of anti-insulin antibodies; the association between such antibodies and severe hypoglycaemia and the suspicion,[23,24] never confirmed, that immune complexes may have contributed to the pathogenesis of microvascular disease.[25,26] We might certainly ask why, if immunogenecity was never a problem, we have invested so much in cleaner and more 'human' insulins over the last 30 years. Meanwhile, this is not an ideal insulin for most people with type 1 diabetes.

Reality check

The decision to use inhaled insulin is thus based solely on the importance to the patient of avoiding injections. Although people say they would be more likely to use insulin if inhaled were an option,[27] this has never been tested in practice. If fear of injections alone puts people off taking insulin, availability of

inhaled insulin should revolutionise our ability to achieve glycaemic control in type 2 patients failing lifestyle and oral therapy, with all the potential advantages in terms of better health sooner. There are no data, however, to show that this will be the case. The insulin requires pre-meal (ie frequent) administration (and the monitoring that mandates) and has never been compared for patient acceptability against a single bedtime injection of an isophane (neutral protamine hagedorn) insulin. There are no data to suggest that pre-meal insulin replacement as first line insulin therapy in type 2 patients is better than background insulin replacement alone. The latter, a simple regimen with minimal risk of hypoglycaemia or weight gain and adjusted according to fasting blood glucose estimations only, is rapidly becoming established as the best way to start insulin in a newly insulin-requiring type 2 patient.

Patient fears of injections will be exacerbated by healthcare professional fears – a large questionnaire study showed that more than 50% of healthcare professionals used insulin as a threat, presumably to encourage greater compliance with other therapies.[28] In such a climate, it is not surprising patients fear insulin. Will the availability of Exubera® change that?

Education is a neglected way of controlling spiralling healthcare costs and we are easily manipulated. Teaching that bedtime injection of peakless analogue insulins is a safe and effective way of starting insulin in type 2 patients has led to a change in the willingness of primary care teams to start insulin therapy and may have contributed to the increasing number of patients achieving Quality and Outcomes Framework targets.[29] That the same result could have been achieved at less than half the cost with conventional insulins[30] underlines the importance of provider belief.

If patients and healthcare providers believe in the ease of use of inhaled insulin, a similar improvement in diabetes control should be repeatable. But given the expense and the potential risk, it would be nice to have the evidence to prove it. Suggesting that inhaling insulin is an easy entry into insulin therapy for people with type 2 diabetes is specious – the patient education and monitoring needed will be the same as for any multiple daily insulin injection regimen. Some pulmonary function monitoring is required, and for the truly insulin dependent, training in the use of injectables either as background or for emergency use, will still be required. At present, healthcare professionals need training too!

Physicians are sceptical about insulin in type 2 patients not just because it involves needles. There are fears of hypoglycaemia, the expense of increased monitoring, the potential for more weight gain and a feeling that, in an obese, sedentary, insulin-resistant patient, it just will not work. Patients fear injections, the unknown, hypoglycaemia, the feeling that they have failed to control their diabetes properly[28] and the knowledge that, historically, insulin was introduced to type 2 diabetic patients when they went into hospital with advanced and disabling complications – and only sometimes came out again. Inhaling the insulin will address none of the foregoing. In contrast, some of the cultural taboos against injection therapy may well be addressed by an inhalable insulin. Fewer than 10% of the patients involved in the clinical trials of Exubera®, however, were non-white. The sad truth is that we just do not know.

We do know that compliance with inhaled medications is not overwhelmingly good, even in chronic lung disease where the effects of the drug are obviously linked to the route of administration. The Exubera® inhaler is not small, requires regular replacement of parts and large doses of insulin can only be taken in multiple inhalations. Some patients injecting at mealtimes may prefer the discretion achievable by the experienced pen injector. The success of the injectable glucagon-like peptide 1 agonist exenatide (marketed under the name of Byetta® in the US), in the same patient group as might be considered for Exubera®, suggests that when a diabetes medication is associated with a much-desired effect such as weight loss, injection therapy is not seen as an insuperable barrier.

So are our insulin requiring diabetic patients condemned to injectable therapy for the foreseeable future? And is NICE simply trying to ration a new therapy for a cash-limited healthcare service? I hope the answer to both these questions is no. Very few people would argue that multiple daily injections of anything are a good thing and the introduction of alternative routes of insulin administration are therefore here to stay. But any new drug for diabetes should be able to offer evidence that it confers positive advantage over older agents without greater hazard, supporting better biomedical outcomes as well as improving quality of life. For those few patients where injection is a real, and major, problem the hazards of inhaled insulin, its lack of biological superiority over older insulins and its expense may be costs worth paying. For everybody else, we lack the proof.

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