Management of type 1 diabetes

Inhaled insulin: What went wrong before and do we need it now?

Daniel Flanagan
Consultant Physician, Derriford Hospital, Plymouth

Bode and colleagues present a clinical paper (summarised alongside) comparing subcutaneous injection of short-acting analogue insulin with a new formulation of short-acting inhaled insulin. The main rationale for the use of inhaled insulin is to reduce hypoglycaemia. The paper is perhaps most interesting, not for what it tells us, but for what it leaves out.

Inhaled insulin is not a new concept. It is only a few years since the launch and subsequent withdrawal of Exubera® (Pfizer). The reason for the withdrawal of Exubera in 2007 was primarily economic; not enough people were using the inhaled product and Pfizer were, therefore, unable to make a profit. The reasons why people did not use the device are more complex. Replacing the need for injections is a significant benefit. Patient surveys repeatedly show that the greatest anxiety at the time of diagnosis is the need to inject but this anxiety is replaced over time by the fear of hypoglycaemia and concerns about complications.

Leaving patient anxiety and fears momentarily to one side, a new way of delivering insulin has to demonstrate three things: Is it safe? Is it more convenient that what is currently available? And is it cost-effective? Safety concerns perhaps come first. Inhaled insulins have previously demonstrated a reduction in lung function and this short-term (24 weeks) study by Bode et al shows the same thing; 6% of people withdrew from the study because of cough. The lungs are highly immunologically active, and previous research has shown an increase in insulin autoantibodies with inhaled insulin, which Bode et al have also shown. The third concern is related to the effects of insulin as a growth factor and the risk of cancer formation in the long term. Convenience is important, but modern insulin pens and needles allow rapid and unobtrusive injection of insulin. One of the major indications for the use of Exubera was needle phobia, but very little mention is made of the current paper.

> *"The paper is perhaps most interesting, not for what it tells us, but for what it leaves out."*

It would not be fair to expect this manuscript to address the question of cost-effectiveness but what we really do need to know is why this product will succeed if others have failed. To be of any interest to clinicians we would like to know if this product stands any reasonable chance of being made available for our patients. ■

Diabetes Care

Inhalable insulin: Safety and effectiveness

Readability	✓✓✓
Applicability to practice	✓
WOW! Factor	✓✓✓

1 The effectiveness and safety of an inhalable insulin, as an alternative to short-acting insulin, was compared to subcutaneous insulin aspart in people with T1D.

2 Inhalable insulin was compared to insulin aspart in an open-label, randomised (1:1) non-inferiority trial lasting 24 weeks among 345 adults already on basal insulin with an HbA_{1c} of 56.8–86.0 mmol/mol (7.5–10.0%) .

3 Individuals in the inhaled insulin group took the dose at the beginning of a meal or up to 20 minutes after starting a meal according to a conversion algorithm (10 units TI-Gen2 per 4 units of insulin aspart). For the first 12 weeks of randomised treatment, prandial doses in each group were adjusted weekly.

4 The mean change in HbA_{1c} from baseline in the inhalable group was non-inferior compared to the injecting group. The between-group difference was also marginal (0.19%) and was lower that the non-inferiority margin of 0.4%.

5 There was a small weight loss of 0.4 kg in the inhalable group compared to a weight gain of 0.9 kg in the injecting group (P=0.0102).

6 A third of the inhalable group experienced coughing, which was the most frequent adverse event during the trial (compared to one fiftieth of the injecting group experienced coughing).

7 The authors conclude that a regimen of inhalable insulin and basal insulin is non-inferior to a standard regimen of basal insulin plus prandial subcutaneous insulin delivery at reducing HbA_{1c}.

Bode BW, McGill JB, Lorber DL et al (2015) Inhaled technosphere insulin compared with injected prandial insulin in type 1 diabetesl. *Diabetes Care* 15 Jul [Epub ahead of print]

Diabet Med

Resources utilised for SH events

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓✓

1 As part of a large phase 3a clinical programme of insulin degludec and insulin degludec/insulin aspart, the frequency and use of care resources for treating severe hypoglycaemia (SH) events (requiring external assistance) were analysed (i.e. use of ambulance or emergency teams, a hospital or A&E visit ≤24 hours, or a hospital visit >24 hours).

2 A large cohort of over 8000 people from 15 clinical trials with T1D and T2D were included. Individuals were on a variety of insulin regimens and 536 SH events were recorded and analysed.

3 Throughout the whole cohort, 29.5% of the SH events involved an ambulance or emergency team, 11.6% required an A&E visit of ≤24 hours and 6.7% required a hospital visit of >24 hours.

4 There were fewer SH events among people with T2D than T1D; however, once a severe episode occurred, the tendency to use health resources and seek assistance was higher in the T2D group compared to the T1D group.

5 The group treated with basal insulin and oral agents required the most hospital care for >24 hours (47.6%) versus the T1D and T2D groups on multiple daily injections (5.0% and 5.3% respectively).

6 The authors conclude that SH often results in emergency or ambulance care, which is a resource and economic burden. Ensuring hypoglycaemia awareness and education is thorough could reduce the use of resources.

Heller SR, Frier BM, Hersløv ML et al (2015) Severe hypoglycaemia in adults with insulin-treated diabetes: impact on healthcare resources. *Diabet Med* 16 Jul [Epub ahead of print]

Diabet Med

Sustained benefit of CSII therapy

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓

1 The clinical records of adults using continuous subcutaneous insulin infusion (CSII) over a 12-year period were analysed for its long-term benefits in lowering HbA_{1c} and hypoglycaemia frequency.

2 Data was collected for 327 people with a mean follow-up of 4.3±2.7 years. At 1 year, HbA_{1c} had fallen by 8±5 mmol/mol (0.7±0.5% [P<0.0005]) and was sustained to year 5.

3 Those that initially had poor glycaemic control at baseline achieved a significant drop in HbA_{1c} at year 1, and this was maintained to year 6.

4 To begin with, 24 people had hypoglycaemia unawareness, but after follow-up, 9 people had regained awareness.

5 The study showed that the CSII can improve hypoglycaemia unawareness and maintain HbA_{1c} improvement.

Beato-Víbora P, Yeoh E, Rogers H et al (2015) Sustained benefit of continuous subcutaneous insulin infusion on glycaemic control and hypoglycaemia in adults with type 1 diabetes. *Diabet Med* **32**: 1453–9

Diabetes Care

Eating disorders in girls and women

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓

1 The study analysed longitudinal data among girls and women with T1D to measure the prevalence of disturbed eating behaviour and eating disorders (ED) among this group.

2 In total, 126 girls with T1D participated in a series of seven interview-based assessments of ED behaviour over a 14-year period.

3 Girls were enrolled at late childhood (mean age 11.8±1.5 years) and continued until 23.7±2.1 years. At the last assessment, 71 females were still involved in the study and 32.4% met the criteria for a current ED, and 8.5% had a sub-threshold ED.

4 Among the cohort, the mean age of ED or associated behaviours was 22.6 years, with a mean remission time of 4.3 years.

5 After remission, the probability of recurrence was 53% by 6 years after remission.

Colton PA, Olmsted MP, Daneman D et al (2015) Eating disorders in girls and women with type 1 diabetes: A longitudinal study of prevalence, onset, remission, and recurrence. *Diabetes Care* **38**: 1212–7

Diabetes Care

Adult cognitive impairment

Readability	✓✓✓
Applicability to practice	✓
WOW! Factor	✓✓✓

1 The authors aimed to investigate the presence and correlation of cognitive impairment in middle-aged adults with childhood-onset T1D.

2 Adults with (n=97) and without (n=138) T1D were subjected to extensive neuropsychological tests, and biomedical data had been collected in the years previously for those with T1D.

3 Cognitive impairment status was defined as none, mild or clinically relevant depending on the number of test scores ≥1.5 standard deviation worse than demographically appropriate published results.

4 The prevalence of clinically relevant cognitive impairment was five times higher among participants with T1D than without (P<0.0001). Chronic hyperglycaemia and prevalent microvascular disease may be associated with cognitive impairment.

Nunley KA, Rosano C, Ryan CM et al (2015) Clinically relevant cognitive impairment in middle-aged adults with childhood-onset type 1 diabetes. *Diabetes Care* **38**: 1768–76

> *"Chronic hyperglycaemia and prevalent microvascular disease may be associated with cognitive impairment."*