LANTUS: insulin glargine does not accumulate

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However we look at it and however much time and effort we put into adjusting an insulin regimen, it does not duplicate the insulin secretion of a healthy pancreas. In the normal situation there should be a low level of circulating insulin between meals with a significant rise in insulin post-prandially. For the majority of people who require insulin therapy, the closest we can come to this is with a basal injection of NPH insulin and bolus injections of a short-acting insulin pre-meal (with the exception of those people on insulin pump therapy). The absorption profile of NPH insulin is clearly not ideal, with a peak insulin level seen 4–7 hours after injection. Practically, we can try several things to deal with this peak; having a bedtime snack or allowing blood glucose to run higher in the preceding hours, but these are both examples of having to tailor lifestyle to fit the insulin rather than tailoring the insulin to fit lifestyle. The consequence of ignoring this peak is nocturnal hypoglycaemia with all that this entails.

There are now a number of publications relating to the recently launched insulin glargine, of which Heise et al is the latest. Modifications to the insulin molecule shift the pH, making the insulin less soluble in subcutaneous tissue. After injection, insulin glargine precipitates in the subcutaneous tissue leading to delayed absorption. The benefit appears to be a peakless metabolic effect. Practically, this translates into less nocturnal hypoglycaemia and lower pre-dinner blood glucose. We do not yet have evidence of lowering of HbA_{1c} over and above that seen with NPH insulin. The paper by Heise et al points out the advantages of insulin glargine over previous ultralente preparations – there is much less variability of action and no accumulation with repeated doses. The American experience would suggest that this is a product we will be getting to know well.

THE NEW ENGLAND JOURNAL OF MEDICINE

Anti-CD3 antibody

Readability	✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓✓

1 It has previously been shown that continuous immune suppression temporarily slows the loss of insulin production.

2 This study investigated the effects of an antibody against CD3 on the loss of insulin production in people with type 1 diabetes.

3 Within 6 weeks of diagnosis, 24 patients were assigned either a 14-day course of antibody treatment or no antibody. Subjects were studied for the first year of the disease.

4 After 1 year, insulin production was maintained or improved in 9 of the 12 patients treated with antibody, and in 2 of the 12 controls.

5 After 1 year, two-thirds of the antibody-treated patients had a C-peptide response to the mixed meal tolerance test that was the same as or greater than their response at study entry. By contrast, there was a consistent decline in the C-peptide response in 10 of the 12 controls.

6 Antibody treatment was not associated with any severe side-effects; the most common effects were fever, rash and anaemia.

Herold KC, Hagopian W, Auger JA, Poumian-Ruiz E et al (2002) Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. New Engalnd Journal of Medicine 346 (22): 1692–8

DIABETIC MEDICINE

LANTUS study

Readability	✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 Insulin glargine is a long-acting insulin analogue with delayed absorption into subcutaneous tissue and a duration of action of >24 hours.

2 To determine whether daily injections lead to insulin accumulation and a concomitant decrease in blood glucose, the multiple dose pharmacokinetic properties of insulin glargine were investigated.

3 The study was completed by 15 patients with type 1 diabetes using preprandial insulin lispro.

4 After wash-out, patients were treated over 12 days with a constant daily dose of insulin glargine, and with preprandial insulin lispro.

5 Free serum insulin (FSI) and blood glucose concentrations were assessed hourly after the first, fourth and eleventh injection, after which patients fasted for 24 hours and did not use any insulin.

6 The time course of FSI was comparable on the three pharmacokinetic study days. No changes occurred in any of the pharmacokinetic parameters studied.

7 Insulin glargine did not appear to accumulate after multiple injections over 12 days. Therefore, the predetermined dose will not need to be reduced after commencing treatment because of risk of accumulation.

8 The comparable time course of circulating insulin concentrations after the first, fourth and eleventh injection of insulin glargine, and the nearly identical trough levels 24 hours after these injections, indicate that a steady-state concentration is achieved as early as day 2.

Heise T, Bott S, Rave K, Dressler A et al (2002) No evidence for accumulation of insulin glargine (LANTUS): a multiple injection study in patients with type 1 diabetes. Diabetic Medicine 19: 490–5

'The study stresses the importance of both intervening early to help families negotiate ways of working together, and of finding ways to encourage parents to maintain involvement for longer.'

Family conflict and glycaemic control

Readability	✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 Diabetes treatment impacts on fundamental aspects of daily family life, and an increase in family stress and conflict is a potential consequence of increasingly complex and demanding therapies.

2 This study set out to investigate the relationship between diabetes-related parental behaviours, adherence to blood glucose monitoring, and glycaemic control, in youths (age 8–17 years) with short duration type 1 diabetes.

3 Along with a parent, 104 youths completed the Diabetes Conflict Scale questionnaires and structured interviews.

4 Children (8–12) and adolescents (13–17) had similar durations of diabetes and similar glycaemic control.

5 In both age groups, parental involvement was a significant predictor of adherence to blood glucose monitoring (BGM), with higher diabetes conflict significantly relating to poorer glycaemic control.

6 Parents of younger children were significantly more involved in BGM and insulin treatment tasks than they were with adolescents, despite the subjects having similar durations of diabetes.

7 Despite these age-related differences in parent involvement in diabetes management tasks, there were no differences in the report of diabetes-related conflict.

8 The study concludes by stressing the importance of both intervening early to help families negotiate ways of working together, and of finding ways to encourage parents to maintain involvement for longer.

Anderson BJ, Vangsness L, Connell A, Butler D et al (2002) Family conflict, adherence, and glycaemic control in youth with short duration type 1 diabetes. Diabetic Medicine 19: 635–42

'Long-term glycaemic control was associated with coronary atheromatosis...'

Silent coronary atheromatosis and glycaemic control

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 This study set out to evaluate the prevalence of silent coronary atheromatosis in patients with type 1 diabetes, and to investigate the relationship between coronary atheromatosis and glycaemic control.

2 Coronary atheromatosis was evaluated in patients with type 1 diabetes of long duration who had no symptoms of coronary artery disease.

3 The evaluation was performed using exercise electrocardiograms, quantitative coronary angiography and intravascular ultrasound examinations.

4 Abnormal exercise electrocardiograms were found in 15% of patients, and angiographic diameter stenoses of >50% in one or more of the main coronary arteries were found in 34% of patients.

5 All patients examined with intracoronary ultrasound had developed atherosclerotic plaques with an increased intimal thickness in one of more of the coronary arteries.

6 After adjustment for total cholesterol and age, coronary artery plaque formation (as judged by ultrasound) was significantly related to mean HbA_{1c} level during 18 years.

7 The study therefore demonstrates a high prevalence of silent coronary atheromatosis in type 1 diabetic patients who have no symptoms of coronary heart disease.

8 Long-term glycaemic control was associated with coronary atheromatosis, supporting the hypothesis that an increased HbA_{1c} level over time increases the risk of developing coronary artery disease in type 1 diabetics.

9 Total cholesterol significantly predicted coronary atherosclerosis. Because a reduction of 1 mmol/l in total cholesterol could have a considerable effect, the authors suggest that lipid-lowering medication should be considered at an early stage in the treatment of type 1 diabetes.

Larsen J, Brekke M, Sandvik L, Arnesen H et al (2002) Silent coronary atheromatosis in type 1 diabetic patients and its relation to long-term glycemic control. Diabetes 51: 2637–41

DIABETES

Endothelial dysfunction and folate status

Readability	✓✓✓
Applicability to practice	✓✓
WOW! factor	✓

1 Children and adolescents with type 1 diabetes have lower levels of total plasma homocysteine (tHcy) than do their nondiabetic counterparts.

2 The levels of tHcy are associated with endothelial dysfunction, which occurs early in the development of vascular disease in diabetes.

3 This study assessed endothelial function in children with type 1 diabetes and in controls, using ultrasound assessment of flow-mediated dilatation (FMD) and glyceryl trinitrate (GTN)-dependent brachial artery responses.

4 Levels of markers of endothelial activation, i.e. von Willebrand factor (vWF) and thrombomodulin, were measured in 64 subjects and 52 controls.

5 FMD and the ratio of FMD:GTN-induced dilatation (which is the best measure of endothelial cell function) were lower in diabetics than in controls, indicating greater endothelial dysfunction.

6 In diabetics, red cell folate correlated independently with FMD and the ratio of FMD:GTN-induced dilatation. These findings suggested that folate status is an important factor protecting against endothelial dysfunction.

7 Resting vessel diameter correlated independently with tHcy levels and with height.

8 vWF correlated strongly and independently with HbA_{1c} levels, suggesting that poor metabolic control leads to endothelial activation.

9 Thrombomodulin correlated independently with red cell folate, diastolic blood pressure and creatinine clearance. The negative independent association of thrombomodulin with red cell folate provided further evidence of a protective effect of folate on endothelial function.

10 Neither vWF nor thrombomodulin were significantly different between diabetics and control subjects.

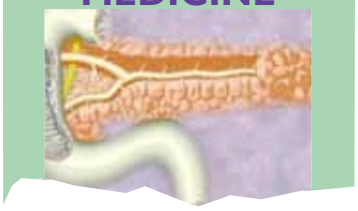
11 Better folate status is associated with better endothelial function (as measured by higher FMD, higher FMD:GTN ratios, and lower thrombomodulin). The authors therefore suggest that folate might protect against endothelial dysfunction in children with diabetes.

12 The study concludes that an intervention trial to assess whether or not folate improves endothelial function in children and adolescents with type 1 diabetes is justified.

Wiltshire EJ, Gent R, Hirte C, Pena A et al (2002) Endothelial dysfunction relates to folate status in children and adolescents with type 1 diabetes. Diabetes 51: 2282–6

'The negative independent association of thrombomodulin with red cell folate provided further evidence of a protective effect of folate on endothelial function.'

DIABETIC MEDICINE



Continuous intraperitoneal insulin infusion

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓

1 The aim of this study was to evaluate the effects of continuous intraperitoneal insulin infusion (CIPII) on glycaemic control and duration of hospital stay in poorly controlled 'brittle' diabetes patients.

2 The subjects studied comprised 33 patients with implantable pumps.

3 Mean HbA_{1c} levels were found to decrease by about 1% 1 year after implantation. They then stabilised at this approximate level during long-term (58 months) follow-up. This value represents a substantial improvement in glycaemic control.

4 The median number of days spent in hospital by the patients decreased from 45 the year before starting CIPII to 13 the year after implantation.

5 After almost 5 years on CIPII, subjects were found to have relatively low levels of quality of life, and there was a higher than expected number of patients with psychiatric symptoms.

6 To summarise, CIPII gave a substantial long-term improvement in glycaemic control and diminished hospital stay, but normal levels of glycaemic control and quality of life were not attained.

7 Overall, for patients with persistent poor control, suffering frequent hospitalisation (e.g. 'brittle' patients, who regularly skip insulin injections), CIPII might be an acceptable mode of treatment.

DeVries JH, Eskes SA, Snoek FJ, Pouwer F et al (2002) Continuous intraperitoneal insulin infusion in patients with 'brittle' diabetes: favourable effects on glycaemic control and hospital stay. Diabetic Medicine 19: 496–501

'For patients with persistent poor control, suffering frequent hospitalisation (e.g. 'brittle' patients, who regularly skip insulin injections), CIPII might be an acceptable mode of treatment.'