Prospective audit of the introduction of insulin glargine (Lantus) into clinical practice in type 1 diabetes

I Gallen, C Carter*

ABSTRACT

The aim of this study was to test whether the reported therapeutic benefits of insulin glargine over older basal insulins are also observed in routine clinical practice.

Eighty-five people with type 1 diabetes were transferred from isophane insulin to insulin glargine between August and December 2002. Selection indications included nocturnal hypoglycaemia, fasting hyperglycaemia, the need for two isophane injections, unusual patterns of receiving insulin therapy or a personal desire to receive insulin glargine. Subject details, including glycaemic control (glucose concentrations and HbA_{1c} levels), were recorded. Questionnaires on the frequency of all hypoglycaemic and severe hypoglycaemic episodes (requiring assistance from a third party) were recorded. Assessments on treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire [DTSQ]), quality of life and well-being (Well-being Questionnaire 28 [W-BQ28]) were also performed. Subjects were re-assessed after receiving insulin glargine for six months.

Morning blood glucose concentrations and HbA_{1c} levels fell significantly, from 9.87±0.39 to 7.93±0.29mM ($p<0.001$) and from 8.24±0.12 to 7.89±0.11 ($p=0.001$), respectively. Total hypoglycaemic episodes remained unchanged after transferral to insulin glargine, but the number of severe hypoglycaemic episodes fell from 18 to two ($p=0.002$). Aggregate DTSQ scores improved from 23.7±0.85 to 28.1±0.87 ($p<0.001$). Perceived energy levels, diabetes specific well-being and total well-being each improved significantly ($p<0.001$, $p=0.006$ and $p=0.032$, respectively).

This study indicates that the therapeutic benefits of insulin glargine reported in clinical trials in type 1 diabetes are also observed in routine clinical practice.

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KEY WORDS

insulin glargine; type 1 diabetes; patient satisfaction surveys; nocturnal hypoglycaemia

People who have type 1 diabetes have the lifelong task of trying to achieve near normal blood glucose values to reduce the chances of developing the disabling complications of diabetes.[1] There are many difficulties in achieving this goal. In addition to the nuisance and perhaps pain of several daily injections of insulin and blood glucose measurements, insulin requirements have to be estimated daily from patterns of food intake, exercise, and the results of blood glucose measurements. Furthermore, the characteristics of absorption of insulin from the subcutaneous tissue after injections vary on an inter- and intra-individual basis, and the time scale of insulin action may not match the patient's daily requirements for insulin.

Insulin glargine is a modified basal insulin analogue that has been introduced recently. Following guidance on the use of long-acting insulin analogues by the National Institute for Clinical Excellence, it is now widely available in the UK.[2] When injected into the subcutaneous tissue, insulin glargine forms a precipitate, which dissociates slowly to form monomers that are able to traverse the capillary membrane and enter the circulation. This results in insulin glargine having a more prolonged and predictable duration of action than older basal insulin preparations.[3] Studies involving people with type 1 diabetes have shown that insulin glargine significantly reduces fasting blood glucose concentrations compared with NPH insulin with at least similar efficacy at reducing HbA_{1c} levels,[4–9] results in significantly fewer episodes of symptomatic and nocturnal hypoglycaemia,[10] and provides improved patient satisfaction.[11]

However, the behaviour and the characteristics of people in study populations may not be the same as those seen in general clinical practice. We have demonstrated previously that the improvement in glycaemic control after the introduction of insulin lispro was greater than that reported in contemporary studies.[12] Therefore, to test whether the reported benefits of insulin glargine can also be achieved in routine clinical practice, we conducted a large, prospective audit of patients attending our diabetes clinic. We identified people with type 1 diabetes who were receiving intensified treatment regimens (i.e. >4 injections of insulin/day) and who had specific problems with their glycaemic control, which were thought to be at least partly due to the action of isophane insulin, and who could, therefore, potentially benefit in being transferred from isophane insulin to insulin glargine.

Ian Gallen, MD, FRCP
Celia Carter, RGN
Diabetes Centre, Wycombe Hospital, High Wycombe, Buckinghamshire, UK

***Correspondence to:** Dr Ian Gallen, Diabetes Centre, Wycombe Hospital, High Wycombe, Buckinghamshire HP11 2TT, UK; e-mail: ian.gallen@sbucks.nhs.uk

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Audit design and methods

Subjects with type 1 diabetes, treated with intensive regimens of multiple daily insulin injections and who were considered suitable candidates for insulin glargine therapy, were identified at their diabetes clinic visits during the period July 2001 to July 2002. These clinics were held at either the Diabetes Centre at Wycombe Hospital, High Wycombe, or the Diabetic Clinic at Amersham Hospital, Amersham. People with specific problems in their glycaemic control, which might in part have been due to the action of isophane insulin, were registered on a computerised audit.[13] These indexed problems were nocturnal hypoglycaemia, morning fasting hyperglycaemia (blood glucose >10mmol/L), the need for two basal isophane injections, shift work or other unusual patterns of insulin therapy, or a personal preference to change to insulin glargine.

Immediately before the introduction of insulin glargine in the UK, registered people were invited to attend one of five multidisciplinary educational seminars led by a diabetes specialist nurse and consultant diabetologist, and were then given instruction on how to transfer to insulin glargine as the basal insulin component. Details on height, weight, glycaemic control (HbA_{1c} level and glucose concentration), the presence of diabetic complications, and insulin type and dosage were obtained from the case notes, in addition to the details of home blood glucose values from the personal record of each participant.

Subjects completed a questionnaire about the frequency of hypoglycaemia, defined as any episode requiring some corrective action by the patient or their carer and confirmed by blood glucose testing; these episodes were recorded over the preceding month. Severe hypoglycaemic episodes were defined as any episode requiring assistance from a third party at any time over the preceding three months. An assessment of perceived treatment satisfaction was made at the start of the audit using the Diabetes Treatment Satisfaction Questionnaire (DTSQ).[14] An assessment of the effect of insulin glargine on the impact of diabetes on the quality of life and well-being was also made using the Well-Being Questionnaire 28 (W-BQ28 and subscale W-BQ12).[15,16] These observations were repeated after six months.

The audit received approval from the local ethical committee. Three people who wanted to use insulin glargine but did not wish to join the audit were similarly instructed and transferred to insulin glargine, but were not included in the data.

Statistical analysis

Statistical analyses of subject demographics, and clinical and biochemical data were performed by paired t test (2-tailed), with analysis on DTSQ and the W-BQ28 by paired t test (2-tailed) confirmed by the Wilcoxon signed rank test. Data from the hypoglycaemia questionnaire were analysed by the Sign test (2-tailed). Data are presented in the text as means (SEM) with the statistical significance of any reported change.

Table 1. Baseline patient data

	Mean	Standard deviation	Minimum	Maximum
Age (years)	38.5	12.4	17.0	72.0
Weight (kg)	80.7	15	50.0	127.5
Height (m)	1.7	0.1	1.6	2.0
BMI (kg/m^2)	27.0	4.3	19.8	43.4
Duration of diabetes (years)	17.6	10.3	1.0	42.0
Total daily insulin dose (units)	63.7	24.6	8.0	135.0

Data derived from 85 patients

Results

Patient details, glycaemic control and hypoglycaemia

Eighty-five subjects with type 1 diabetes were studied for six months, 41 were women, and all were Caucasian except for one South Asian and one Afro-Caribbean person. One person stopped use of insulin glargine. Baseline subject data, including any diabetic complications, are given in Tables 1 and 2. The indications for treatment with insulin glargine are given in Table 3.

After six months of treatment with insulin glargine, mean morning blood glucose concentrations fell from 9.87±0.39 to 7.93±0.29mM ($p<0.001$), and mean HbA_{1c} levels also fell from 8.24±0.12 to 7.89±0.11 ($p=0.001$). This fall in HbA_{1c} was seen with each indication for insulin glargine, with the exception of patient request, where no statistically significant decrease was observed. The reduction in HbA_{1c} was similar for men and women and for younger and older people (above or below 40 years

Table 2. Complications of diabetes in the study population

	Number	Percentage
Retinopathy	34	40%
Nephropathy	10	12%
Lipodystrophy	7	8%
Cardiovascular disease	8	10%
Neuropathy	5	6%
Other vascular disease	1	1%
Foot disease	1	1%
Erectile dysfunction (n=38)	6	16%

Except where specified, data derived from 85 patients

Table 3. Indications for transferring to insulin glargine

	Number	Percentage
Nocturnal hypoglycaemia	45	57%
Marked dawn phenomenon	41	52%
Two basal insulin injections/day	10	13%
Patient request	28	35%

Data derived from 85 patients

of age). However, significantly reduced HbA_{1c} levels were seen only in subjects with initial values above 8% and BMI >27/kg/m^2 (Table 4). Total episodes of hypoglycaemia remained unchanged at around five per week, but the total reported episodes of severe hypoglycaemia (requiring assistance from a third party) fell from 18 to two (p=0.002) at six months. No change was seen in weight or in total insulin dose.

Patient reported outcomes

Aggregate scores for the DTSQ (questions 1 and 4–8), which reflect satisfaction with treatment, improved from 23.7±0.85 to 28.1±0.87 (p<0.001), whereas scores reflecting dissatisfaction with glycaemic control (questions 2 and 3) fell from 3.6±0.19 to 2.7±0.21 (p<0.001) for unacceptably high blood sugar values, but no change was seen for unacceptably low blood sugar values. Aggregate scores for the DTSQ increased with the indications of nocturnal hypoglycaemia (23.9±1.1 to 28.2±1.2, p=0.022) or marked dawn phenomenon (24.7±1.2 to 28.9±1.1, p=0.009), but not for patient request. Scores for unacceptably high blood sugar values fell for people with the indications of either nocturnal hypoglycaemia (3.8±0.2 to 2.6±0.2, p<0.001) or marked dawn phenomenon (3.6±0.3 to 2.5±0.3, p<0.001), but not for patient request. No differences were seen for unacceptably low blood sugar values between the treatment indication sub-groups.

Details of the scores for W-BQ28 are given in Table 5. These data show significant improvements in patients' reported energy levels (p<0.001), diabetes-specific well-being (p=0.006), and measure of total well-being, the W-BQ12 standard scale (p=0.032), with no

Table 4. Effect of insulin glargine treatment on HbA_{1c}

	Patients (n)	Baseline*	6 months*	Change from baseline*	Statistical significance
HbA_{1c}	78	8.24 (0.16)	7.76 (0.11)	-0.38 (0.13)	p=0.006
HbA_{1c} by age					
<40 years	34	8.21 (0.17)	7.76 (0.15)	-0.46 (0.12)	p<0.001
≥40 years	39	8.27 (0.18)	8.0 (0.15)	-0.27 (0.13)	p=0.044
HbA_{1c} by gender					
men	35	8.27 (0.20)	7.81 (0.16)	-0.46 (0.14)	p=0.003
women	38	8.22 (0.15)	7.96 (0.14)	-0.27 (0.11)	p=0.021
HbA_{1c} by baseline HbA_{1c}					
<8mmol/L	31	7.35 (0.08))	7.27 (0.08)	-0.1 (0.1)	p=0.33
≥8mmol/L	42	8.89 (0.14)	8.34 (0.14)	-0.55 (0.13)	p<0.001
HbA_{1c} by baseline fasting blood glucose					
<10mmol/L	30	8.0 (0.16)	7.71 (0.17)	-0.29 (0.09)	p=0.029
≥10mmol/L	30	8.46 (0.23)	8.01 (0.158)	-0.45 (0.15)	p=0.006
HbA_{1c} by indication					
nocturnal hypoglycaemia	37	8.26 (0.175)	7.89 (0.16)	-0.37 (0.1)	p=0.001
marked dawn phenomenon	36	8.1 (0.17)	7.76 (0.14)	-0.34 (0.12)	p=0.010
patient request	26	8.34 (0.23)	8.07 (0.218)	-0.26 (0.17)	p=0.14
HbA_{1c} by baseline BMI					
<27kg/m^2	43	6.8 (0.6)	7.1 (0.2)	+0.3 (0.8)	p=0.77
≥27 kg/m^2	28	8.15 (0.14)	7.82 (0.139)	-0.33 (0.1)	p=0.002

*Data are means (SEM)

Table 5. Results from patient well-being questionnaire (W-BQ28)

W-BQ28 subscale	Change	SEM	Statistical significance
Negative well-being	-0.23	0.19	NS
Energy	0.97	0.23	p<0.001
Total well-being (W-BQ12 standard scale)	1.28	0.58	p<0.032
Stress	-0.17	0.22	NS
Diabetes-related stress	-0.27	0.28	NS
Diabetes-related negative well-being	-0.14	0.19	NS
Diabetes-related positive well-being	0.97	0.33	p=0.006

change in reported perceptions of generic stress or diabetes-related stress. Improvement in reported energy levels was seen in people with either nocturnal hypoglycaemia (5.0±0.5 to 6.0±0.5, p=0.014) or marked dawn phenomenon (5.1±0.5 to 6.2±0.5, p<0.004), but not for patient request.

Discussion

People with diabetes require treatment with a combination of short acting and intermediate to long acting insulin to optimise glycaemic control. Isophane/NPH insulin is most commonly used, but has wide intra- and inter-patient variability in the pattern of release of insulin from depots, and may produce somewhat unpredictable physiologic action. It has a peak level of action that occurs between four and six hours after injection and has a limited total duration of action of around 12 hours. The effect of this pattern of release is that there is a relative excess of insulin overnight and a relative deficiency of insulin in the morning. Increasing prebedtime insulin dosage, to reduce morning blood glucose concentrations, often results in nocturnal hypoglycaemia, which is a major limiting factor in achieving optimal glycaemic control.[17]

Insulin glargine is a modified basal insulin analogue that precipitates on injection into the subcutaneous tissue. This precipitate dissociates slowly to form monomers that are able to traverse the capillary membrane and enter the circulation. As a result, insulin glargine has a more prolonged and predicable duration of action.[3] Clinical trials of people with type 1 diabetes have shown that insulin glargine, compared with NPH insulin, lowers fasting blood glucose concentrations and HbA_{1c} levels,[4–9] with fewer episodes of symptomatic and nocturnal hypoglycaemia,[5,10] and improved patient satisfaction.[11]

This prospective clinical audit documents the results of transferring people with type 1 diabetes, treated with multiple daily injected insulin therapy, from isophane insulin to insulin glargine as their basal insulin component. Our results show that, on average, people who transfer from isophane insulin can reasonably expect to have a significant fall in their morning blood glucose concentrations and HbA_{1c} levels. However, subjects who were thinner, or who had relatively good glycaemic control, did not seem to improve their control further. We found that people had fewer episodes of severe hypoglycaemia, although the total number of hypoglycaemic episodes was similar. The DTSQ shows a significant improvement in patient satisfaction with their treatment following transfer to insulin glargine from isophane insulin. There was also a fall in the perception of unacceptably high blood glucose concentrations. The W-BQ28 demonstrates improvement in energy levels, and diabetes-related positive well-being with insulin glargine, compared with isophane insulin. The measure of total well-being, the W-BQ12 standard scale, improved and these results are directly comparable with previous reports.[11] No change was seen with diabetes-related stress, diabetes-related negative well-being or stress. There did not seem to be any counterbalancing negative effects. Furthermore, after the initial instruction period, patients did not have to do any further work to improve their glycaemic control over and above their existing self-management of diabetes.

This audit did not have a control group and an alternative explanation for the improvement seen in glycaemic control, hypoglycaemia and perceived satisfaction with treatment and energy levels might be that a period of re-education by the diabetes specialist nurse and renewed interest by the subjects have effected these beneficial changes. However, subjects who requested transfer to insulin glargine, but in whom no specific indication was present, did not improve glycaemic control, or have increased satisfaction with their treatment or improved energy levels. This group of subjects' experience supports the suggestion that the beneficial effect of insulin glargine is more than just a study effect.

In conclusion, this audit confirms that the therapeutic benefits of insulin glargine over NPH insulin that were observed in clinical trials of patients with type 1 diabetes – namely improved glycaemic control, a reduced risk of hypoglycaemia and improved patient satisfaction – are also seen in routine clinic practice. Our data suggest that many people with type 1 diabetes are likely to benefit by being transferred from their current basal insulin to insulin glargine.

Key points

- Insulin glargine therapy in type 1 diabetes reduces HbA_{1c} and morning blood glucose
- Insulin glargine therapy reduces nocturnal hypoglycaemia
- Insulin glargine therapy is associated with improvement in treatment satisfaction and well-being

Conflicts of interest

South Buckinghamshire Diabetes Research Fund funded the audit. Buckinghamshire Hospitals NHS Trust employs Dr Gallen and Mrs Carter. Dr Gallen has received speaker fees from Aventis Pharma.

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Letter. Unusual failure of a pre-filled glucose syringe during treatment of hypoglycaemia

Sir, We would like to draw the attention of readers to an episode of severe hypoglycaemia that occurred during the management of diabetic ketoacidosis and the unusual mechanical failure of a pre-filled glucose syringe which hampered resuscitation.

A 78-year-old woman with diabetic ketoacidosis was receiving intravenous insulin (1–6 units per hour of Actrapid according to a sliding scale) and 5% glucose. Both infusions were linked together by a 'Y' connection and attached to a 20-gauge cannula (Optiva 2 by Johnson and Johnson) located in a peripheral vein. Severe hypoglycaemia unexpectedly occurred with a blood sugar of less than 1mmol/L. Injection of 50% glucose in a 50ml 'mini-jet' pre-filled syringe through the dorsal port of this small cannula proved difficult as the solution was very viscous. The infusion line was then disconnected and the same pre-filled glucose syringe was directly attached to the venous cannula. At this stage the distal tip of the plastic syringe snapped off completely and became firmly embedded in the end of the cannula (see Figure 1).

The resultant total loss of contiguity rendered it impossible to inject the pre-filled glucose or reconnect the glucose infusion. Another venous cannula was quickly inserted to allow glucose administration and fortunately no harm came to the patient during this delay.

In the above clinical scenario, the injection of a viscous solution of 50% glucose from the pre-filled syringe through the dorsal port of the venous cannula must have required a modicum of downward force. Attaching the same syringe to the free end of the cannula would only require a gentle twisting action. We wondered if the syringe's inner metal spike had sheared off the encasing plastic tip during these manoeuvres. However, several attempts by us proved unsuccessful in replicating this