New approaches to insulin prescribing in primary care

Roger Gadsby and Geralyn Spollett

ARTICLE POINTS

1 Primary healthcare professionals play an important part in diabetes management.

2 Insulin glargine is the first long acting basal insulin analogue to be available in the UK.

3 It is important that UK healthcare professionals draw on the experience of their US counterparts in using insulin glargine

4 Insulin glargine offers potential benefits to both patients and healthcare professionals

KEY WORDS
- **Insulin glargine**
- **Hypoglycaemic event**
- **Carbohydrate counting**
- **24 h coverage**
- **Lifestyle flexibility**

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Introduction

The incidence of type 2 diabetes continues to rise sharply in both the UK and US due to growing levels of obesity and an ageing, and increasingly sedentary, population. The increase in patient numbers and concerns about how to cope with this 'avalanche' of diabetes led to the recent establishment of a National Service Framework (NSF) for Diabetes, which aims to achieve improved glycaemic control and reduce morbidity. A further consequence of this increase in patient numbers is that primary healthcare professionals now play an important part in diabetes management including the initiation of insulin treatment in type 2 diabetes.

Insulin glargine is the first long acting basal insulin analogue. It was made available for clinical use in the UK on 28 August 2002, but has been used widely in the US since May 2001. The only other long acting basal insulin analogue, insulin detemir, is currently in phase III clinical trials and is expected to be launched in the next few years. Insulin glargine is indicated for diabetes where treatment with insulin is required. It would be helpful for primary healthcare professionals in the UK to learn from experience that their US colleagues have gained with insulin glargine. In in this article we offer practical advice by drawing on US experience.

Properties of insulin glargine

Insulin glargine differs from human insulin at three amino acid residues: two arginine residues have been added to the C-terminus end of the B-chain and an asparagine has been substituted for a glycine at position 21 of the A-chain (Owens et al, 2001; Rosskamp and Park, 1999). The changes made to the molecule mean that it is soluble in slightly acidic conditions and crystallises in the neutral pH of the subcutaneous tissue. Absorption is therefore delayed and a constant 'peakless' basal insulin supply is produced for 24 h, similar to that observed with continuous subcutaneous insulin infusion (CSII), enabling once daily administration (Heineman et al, 2000; Pieber et al, 2000; Raskin et al, 2000; Ratner et al, 2000; Rosenstock et al, 2001; Rosenstock et al, 2000; Yki-Järvinen et al, 2000). Inter-patient variability is less with insulin glargine than with neutral protamine hagedorn (NPH) and ultralente (Lepore et al, 2000) and intra-patient variability is also less than with ultralente (Porcellati et al, 2001; Scholtz et al, 1999).

Practical points on administering insulin glargine

Insulin glargine is available in 10 ml vials (equivalent to 1000 IU), in cartridges (used with the reusable insulin pen, OptiPen Pro®) containing 3 ml of insulin glargine (equivalent to 300 IU) and in pre-filled disposable pens (OptiSet®) also containing 3 ml. Administration is once a day by subcutaneous injection in the evening. Insulin glargine should not be mixed with other insulins or diluted. Because insulin glargine is the first clear, long acting insulin, the patient does not have to shake the vial before injecting. Dosage should be adjusted on an individual basis.

Clinical experience

The level of glycaemic control obtained with insulin glargine is equivalent to, and in some cases better than that achieved when using NPH insulin (Pieber et al, 2000; Yki-Järvinen, et al 2000). However, patients receiving insulin glargine have fewer hypoglycaemic episodes, particularly

nocturnal episodes (Ratner et al, 2000; Yki-Järvinen et al, 2000). The peakless profile of insulin glargine is thought to be responsible for this.

Additionally, insulin glargine has been shown to enable most patients with type 2 diabetes, who were inadequately controlled with oral hypoglycaemic agents (OHAs), to reach target HbA_{1c} levels of 7%, with a significantly lower risk of hypoglycaemia than with NPH (Riddle and Rosenstock, 2002). Furthermore, absorption rates of insulin glargine at the main subcutaneous sites of injection are similar, unlike other basal insulins (Owens et al, 2000).

There is some evidence that insulin glargine may be associated with less weight gain than NPH. This could be linked to the reduced risk of hypoglycaemia as patients who fear a hypoglycaemic event usually eat in an attempt to prevent it (Raskin et al, 2000; Rosenstock et al, 2001). As a probable result of these features, it has been reported that patients who were switched from NPH insulin to insulin glargine were more satisfied with their treatment compared to patients who remained on NPH insulin (Witthaus et al, 2001).

US experience

In this section we describe two patient case studies, one with type 2 diabetes and the other with type 1 diabetes, for whom treatment with insulin glargine was judged appropriate and who have been effectively switched to regimens that include this new form of insulin.

Case study 1

Fran, aged 56 years was diagnosed with type 2 diabetes 6 years ago. Her body mass index was 33 kg/m^2, her blood pressure was 144/84 mmHg and her last HbA_{1c} reading was 7.8%. She was being treated with the following oral agents: 1 000 mg metformin twice a day; 4 mg glimepiride once a day; and 10 mg atorvastatin once a day. Fran plays golf twice a week and tends her garden for 2–4 h per week. She was measuring her carbohydrate intake and followed a diet prescribed by a dietitian.

Fran monitored her blood glucose twice a day, but had recently increased this to four times a day because of high readings (*Table 1*). Her highest blood glucose values were at breakfast, and were still over target at lunchtime. As she needed to improve her glucose control, particularly overnight, we decided that proactive insulin therapy should be initiated to reduce glucose levels during the night and to provide better meal coverage.

Table 1. Fran's SMBG log while on oral treatment only

Blood glucose concentrations during the day (mmol/L)				
Day	Breakfast	Lunch	Supper	Bedtime
Monday	13.11	9.22	7.44	8.72
Tuesday	11.78	9.94	6.78	8.0
Wednesday	15.44	6.78	7.39	9.39

Table 2. Fran's SMBG log when receiving insulin glargine (IG) treatment

Blood glucose concentrations during the day (mmol/L)					
Day	Dose of IG (IU)	Breakfast	Post-breakfast	Pre-supper	Post-supper
Sat	14	7.44	6.22	7.33	8.56
Sun	14	6.61	7.44	6.89	9.28
Mon	14	6.83	7.78	6.28	8.06
Tues	16	5.89	5.44	6.61	8.22

SMBG = self-monitoring of blood glucose

The new management choices for insulin therapy were NPH at bedtime, a mixed dose at supper (75/25 or 70/30 premix), or insulin glargine at bedtime. Before deciding on the most suitable insulin regimen for Fran, a few factors had to be taken into account. She had irregular evening meals, which influenced her bedtime blood glucose. She wanted to try a bedtime insulin dose for convenience, but was concerned about weight gain associated with insulin therapy.

We chose insulin glargine as the basal insulin, as it would provide the 24 h coverage that Fran needed and also because it was associated with less average weight gain than other basal insulins (Raskin et al, 2000; Rosenstock et al, 2001). We started treatment at 10 units at bedtime, which was then titrated to 16 units (*Figure 1*; Barnett et al, 2002). Titration is based on fasting glucose concentrations if no signs or symptoms of

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1 Patients who switched from NPH insulin to insulin glargine were more satisfied with their treatment compared to patients who remained on NPH insulin.

2 Insulin glargine provides 24 h coverage and is associated with less average weight gain than other basal insulins.

Table 3. Elena's insulin regimen before switching to insulin glargine

Time of dose	Insulin regimen (IU)
Breakfast: 07:00–08:00	lispro 3–7 and NPH 22
Supper: 18:00–20:00	lispro 5–8 (adjusted according to her SMBG)
Bedtime:23:00–24:00	NPH 16

hypoglycaemia are detected and self-monitoring of blood glucose (SMBG) must be done more frequently until glucose levels approach target. Therefore, as well as her usual fasting breakfast and pre-supper tests, Fran also had to include post-breakfast and post- supper tests (*Table 2*). In addition (as with all insulin initiations) Fran received nutritional advice and guidance. All oral agents were initially retained, although sulphonylureas may be dropped as control improves. Fran was concerned about the weight gain associated with insulin therapy, so it was important to retain metformin in the regimen, as insulin has been associated with less weight gain when used with metformin than when used alone (Yki-Järvinen, 2001).

If insulin therapy with insulin glargine alone is not sufficient to achieve targets, then rapid-acting insulins (such as aspart or lispro) could be added to the regimen. For Fran, insulin glargine was generally effective at lowering blood glucose levels throughout the day, with a reduced risk of hypoglycaemia and without causing significant weight gain.

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3 Insulin glargine mimics endogenous insulin basal patterns.

Case study 2

Elena was a 28-year-old postgraduate student with type 1 diabetes. She had been receiving intensive insulin therapy for 3 years and experienced multiple hypoglycaemic events, particularly in the late afternoon and early evening. Her HbA_{1c} levels fluctuated from 6.8–7.5%. Elena's original insulin regimen is detailed in *Table 3*. She used exchange diet/menu selections (a system whereby carbohydrate content and size of meals is monitored but which does not involve a strict calorie-restricted diet) and walked to and from classes with no other exercise regimen. Her SMBG log is shown in *Table 4*.

Elena had several problems with her original therapy. The regimen was very inflexible which was inconvenient as her variable university schedule meant that her meal times were irregular. NPH had the disadvantage of peaking early some days, and provided limited evening coverage. As a consequence Elena experienced hypoglycaemic episodes. In an attempt to avoid these Elena raised her calorie intake, which caused her to gain weight and increased her HbA_{1c} levels. The diet system that she had been following also offered little flexibility.

For Elena, switching from NPH to insulin glargine was advantageous in that insulin glargine mimics endogenous insulin basal patterns. It eliminates the problematic 'peak' observed with NPH which can cause hypoglycaemia, and therefore reduces the risk of a hypoglycaemic event. Insulin glargine thus provided greater flexibility, ideal for her variable lifestyle.

Table 4. Elena's SMBG log before the switch to insulin glargine

	Blood glucose concentrations during the day (mmol/L)				
Day	Breakfast	Lunch	Supper	Bedtime	Information
Mon	6.7	-	2.38	12.5	Soda x 2
Tues	7.55	5.72	4.8	7.1	
Wed	5.55	4.27	2.94	16.1	Food!
Thurs	10.3 / 21U*	6.77	8.55**	9.22	
Fri	6.27	6.72	3.38***	10.38	
			7.38		

* Insulin lispro needed
** Pizza
*** Late supper so two readings
- Blood glucose recordings not taken

Guidelines for switching to insulin glargine

(In all cases, glucose concentrations should be measured before breakfast and at bedtime)

Patient new to insulin therapy

(1) Initiate insulin glargine e.g. 12 IU at bedtime

(2) Titrate appropriately

Patient on NPH insulin once daily

(1) Convert directly to insulin glargine at same total daily dosage

(2) Titrate appropriately

Patient on NPH insulin twice daily

(1) The starting dose of once daily insulin glargine at bedtime should be 20% lower than the previous total daily dose of NPH

(2) Once insulin glargine is initiated, titrate dose appropriately to meet glucose targets

Figure 1. Guidelines for switching to insulin glargine (Barnett A H et al, 2002).

Following the guidelines in *Figure 1*, the steps involved in switching Elena from NPH to glargine were as follows:

- Total daily dose of NPH: 38 IU (22 IU+16 IU).
- Total NPH reduced by 20%: 7.6 IU.
- 38 –7.6 IU = 30.4 IU (insulin glargine).
- Insulin glargine 30 IU started at 23:00.

Elena's SMBG log after the switch is shown in *Table 5*. On switching to insulin glargine, it was important to remind Elena to continue testing her fasting glucose in order to make the necessary adjustments to the insulin glargine dose. An extra lunchtime bolus was needed to prevent post-meal hyperglycaemia. In such a case, it may also be necessary to adjust all pre-meal lispro doses to take into account the different profile that insulin glargine offers compared with NPH. A further point highlighted to Elena was that carbohydrate counting may offer greater flexibility and easier decision making for meal coverage.

Once the insulin glargine therapy was established, and as her fasting glucose improved, Elena's pre-meal blood glucose was evaluated to adjust the insulin glargine as necessary, in order to reach post-meal targets. An insulin dose/carbohydrate level ratio system was recommended and was successfully implemented. This is a similar system to the Dose Adjustment For Normal Eating (DAFNE) programme used in the UK. Elena is satisfied with her insulin

PAGE POINTS

1 Carbohydrate counting may offer greater flexibility and easier decision making for meal coverage.

2 Insulin glargine offers the patient 24 h coverage, less risk of hypoglycaemia, the possibility of achieving HbA_{1C} targets and a greater lifestyle flexibility.

3 In the US, insulin glargine is becoming the basal insulin of choice for people with type 1 diabetes.

Table 5: Elena's SMBG log after the switch from NPH to insulin glargine

		Blood glucose concentrations during the day (mmol/L)			
Day	Dose of IG (IU)	Breakfast Post-breakfast	Lunch Post-lunch	Supper Post-supper	Bedtime
Tues	30	8.55 9.27	6.77 -	- 9.83	8.66
Wed	30	7.77	6.16 7.16	7.44 -*	6.77
Thurs	30	7.38	7.0 4.88	6.22** -	9.27
Fri	32	6.83 6.5	7.77 -	6.5 7.6	7.16

IG = insulin glargine * run ** late meal - blood glucose recordings not taken

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1 Insulin glargine offers the patient 24h coverage, a flat profile with less risk of hypoglycaemia, the possibility of achieving HbA1c targets and greater lifestyle flexibility.

2 The experience gained by healthcare professionals in the US at switching patients to insulin glargine will prove useful to UK healthcare professionals.

glargine regimen as it is more convenient, allowing her greater flexibility and has reduced her fear of experiencing hypoglycaemic episodes.

Conclusion

Insulin glargine is a great improvement in insulin treatment as it offers the patient 24 h coverage, a flat profile with less risk of hypoglycaemia, the possibility of achieving HbA_{1c} targets and greater lifestyle flexibility. The experience gained by healthcare professionals in the US at switching patients to insulin glargine will prove useful to UK healthcare professionals in implementing such treatments here. In the US insulin glargine is becoming the basal insulin of choice for people with type 1 diabetes, and is used as the ideal once-daily insulin to be added to oral agent treatments when tablets alone are not giving optimal glycaemic control in people with type 2 diabetes. ■

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