Insulin glargine: a new basal insulin analogue

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Introduction

Currently, the therapeutic challenges in the treatment of both type 1 and 2 diabetes mellitus (DM) are the maintenance of near-normal glycaemia, to prevent long-term complications,1,2 and the avoidance of episodes of hypoglycaemia. For many people with DM, intensive insulin therapy means multiple insulin injections and frequent blood sampling, at the expense of an increased risk of hypoglycaemia. This article will discuss the potential use of a new long-acting insulin analogue, insulin glargine, already prescribed in the US but expected to be available in the UK later this year.

Normal insulin secretion consists of discrete components: low basal levels secreted between meals, through the night and during fasting; and very high levels secreted post-prandially (Figure 1). Basal-bolus insulin regimens attempt to reproduce this insulin secretion profile, which consists of one or two injections per day of intermediate or long-acting insulins (basal) and multiple meal-time (bolus) injections of rapid-acting or regular insulins.

The disadvantages of conventional insulin preparations include variable absorption with considerable intra and inter-subject variation, pronounced peaks after injections, and prolonged duration of action, all contributing to the difficulty in obtaining normoglycaemia (Table 1). Hypoglycaemia is the limiting factor in the maintenance of tight glycaemic control.3 Hypoglycaemia ranks high among the fears of patients using insulin, resulting in a decrease in quality of life, reduced awareness of subsequent hypoglycaemia and thereby increased risk of severe hypoglycaemia.4,5

Rapid-acting insulins

The late 20th century has seen the development of genetically engineered human insulins. The first rapid-acting insulin analogue, insulin lispro, was introduced into clinical practice in 1996. The analogue was developed in an attempt to make the pharmacokinetic profile of injection more like its normal physiological counterpart, and thereby to better normalize glucose excursions following meals.

The effectiveness of rapid-acting insulin analogues in controlling post-prandial glycaemia has...
been demonstrated in many clinical studies. Their use also allows for the convenience of injecting closer to meals, or even post-prandially. In addition, reduced frequency of hypoglycaemic episodes has been observed with insulin lispro compared to conventional short-acting insulins. Improvements in overall glycaemic control was not seen in the short-term trials, nor in the first of the long-term trials of insulin lispro compared with short-acting insulins. However, some later studies, designed to examine the effect of insulin lispro on HbA1c, and which directed attention toward adjusting the basal insulins, demonstrated the ability of insulin lispro to provide lower HbA1c levels with fewer hypoglycaemic episodes. Thus it appears that glycaemic control in the long term is dependent on the extent to which basal insulin is optimized.

### Conventional basal insulins

Conventional intermediate and long-acting insulins have an onset of action of 0.5–4 h, a maximal effect at 4–20 h and a duration of 8–36 h (Table 1). The absorption pattern of conventional long- and intermediate-acting insulins put many patients at risk of nocturnal hypoglycaemia, despite avoidance measures such as a bedtime snack or taking the basal insulin later at bedtime. As the effect of the evening dose of insulin wanes towards the morning, some patients may develop hyperglycaemia. Even the longest-acting human insulin preparation, ultralente, produces a peak insulin level at between 12 and 16 h, and often does not provide adequate basal insulin supplementation when injected once daily. These factors contribute to the instability of blood glucose with fluctuations from hypoglycaemia especially at night and to hyperglycaemia, particularly in the fasting state. Nocturnal hypoglycaemia occurs in up to 40% of patients with type 1 DM, and often leads to a failure to achieve good glycaemic control. Thus the clinical challenge is to find a dose of insulin sufficient to control the fasting blood glucose without causing nocturnal hypoglycaemia.

### Insulin glargine

Insulin glargine is a new long-acting insulin analogue. Developed by recombinant DNA technology, it has amino acid changes in both the A and B chain of the molecule, compared to human insulin. This leads to a shift of the isoelectric point towards a neutral pH, resulting in a molecule that is less soluble at the injection site and precipitates subcutaneously to form a depot, from which insulin is slowly released. The time action profile lacks the pronounced peak that occurs with isophane insulin, thus mimicking a more physiological insulin secretion as in non-diabetic subjects. The use of glargine as the basal insulin should be combined with the rapidly acting insulins such as insulin lispro or insulin aspart as the bolus insulin, so as to mimic the physiological insulin secretion pattern as closely as possible, particularly in individuals with type 1 DM who have no endogenous insulin production.

A disadvantage of insulin glargine is that, unlike isophane insulin, it cannot be mixed with soluble insulins as this results in precipitation. Thus many patients with biphasic (mixture) insulins will be required to increase their number of daily injections and/or change to a basal-bolus injection regimen. It is unlikely that all patients will be willing to do so.

### Table 1 Pharmacokinetics of current insulin preparations

<table>
<thead>
<tr>
<th>Type of insulin</th>
<th>Onset</th>
<th>Peak effect</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro (Humalog)</td>
<td>0–15 min</td>
<td>30–90 min</td>
<td>&lt;5 h</td>
</tr>
<tr>
<td><strong>Short acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular human insulin (Humalin S, Actrapid)</td>
<td>30–45 min</td>
<td>2–4 h</td>
<td>6–8 h</td>
</tr>
<tr>
<td><strong>Intermediate acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semilente</td>
<td>0.5–1 h</td>
<td>4–6 h</td>
<td>8–12 h</td>
</tr>
<tr>
<td>Lente</td>
<td>2–4 h</td>
<td>6–10 h</td>
<td>12–24 h</td>
</tr>
<tr>
<td>Isophane</td>
<td>2–4 h</td>
<td>6–10 h</td>
<td>12–24 h</td>
</tr>
<tr>
<td><strong>Long acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultralente</td>
<td>3–4 h</td>
<td>8–20 h</td>
<td>20–36 h</td>
</tr>
<tr>
<td>Protamine zinc</td>
<td>3–4 h</td>
<td>14–20 h</td>
<td>24–36 h</td>
</tr>
</tbody>
</table>
Clinical trials using insulin glargine

Insulin glargine has been compared to isophane insulin in several large clinical trials in both type 1 and 2 DM. The trials were not blinded, as insulin glargine is a clear solution, unlike other conventional intermediate or long-acting insulins that form a cloudy suspension.

Type 1 diabetes mellitus

In a multi-centre trial involving 534 patients with well-controlled type 1 DM, randomized to either insulin glargine or isophane for up to 28 weeks, the incidences of all symptomatic hypoglycaemic episodes were similar between both of the study groups. However, there were fewer episodes of severe hypoglycaemia and nocturnal hypoglycaemia where blood glucose was <2.0 mmol/l in the patients taking glargine. No significant changes in glycaemic control were found in the two groups, although there was a greater reduction in median fasting plasma glucose in the insulin glargine group.

A similar trial involving 333 patients with type 1 DM over 4 weeks also found a lower fasting plasma glucose and incidence of nocturnal hypoglycaemia in patients using insulin glargine compared to isophane insulin. However, the overall frequency of hypoglycaemia did not differ, and the lower incidence of nocturnal hypoglycaemia was significant only versus isophane insulin once daily, not twice daily. A significant beneficial effect on lowering of HbA1c was observed in the insulin glargine group.

A phase III randomized 16-week open-label study of 619 patients with type 1 DM using basal treatment with isophane insulin and lispro were randomized to receive insulin glargine daily or isophane twice daily. The reported incidences of asymptomatic and severe hypoglycaemia (<2.0 mmol/l) were similar in both groups. Nocturnal hypoglycaemia was more frequent in patients using insulin glargine compared to patients taking isophane insulin (69% vs. 63%, p = 0.06).

Insulin glargine has been studied in 349 children/adolescents aged between 5–16 years with type 1 DM. They were randomized to either insulin glargine or isophane insulin. Regular short-acting insulin was used in both groups pre-meal. There were no significant differences in insulin glargine and isophane in terms of change in HbA1c, although fasting plasma glucose was lower in the insulin glargine group. The overall incidences of hypoglycaemia were similar in both groups. There was a reduced incidence of severe and nocturnal hypoglycaemic episodes in the glargine group, but this did not achieve statistical significance.

Insulin glargine had superior treatment satisfaction scores, psychological well-being benefits and lower perceived frequency of hypoglycaemic episodes, compared to isophane insulin, in 517 patients with type 1 DM participating in a randomized control trial.

Type 2 diabetes mellitus

Yki-Jarvinen et al. studied 426 patients with type 2 DM with poor glycaemic control on oral antidiabetic agents who were randomized to receive either isophane insulin or insulin glargine at bedtime in addition to continuation of their oral agents. Although no difference was found in glycated haemoglobin, patients randomized to insulin glargine had a lower incidence of symptomatic hypoglycaemia, nocturnal hypoglycaemia and a lower fasting plasma glucose than patients using isophane insulin.

In a 28-week study, 518 patients with type 2 DM who were receiving isophane insulin, with or without regular insulin for post-prandial control, were randomized to receive either isophane insulin or insulin glargine as the basal insulin, with or without additional regular insulin before meals. No significant differences in HbA1c and symptomatic hypoglycaemia in both groups were found. However the incidence of nocturnal hypoglycaemia was significantly lower in the insulin glargine group.

Adverse effects

Injection site pain was more frequently reported in patients treated with insulin glargine than isophane insulin in some studies, but not invariably.
This may relate to the acidity of the solution compared to conventional insulin. Insulin glargine has a six-fold higher affinity to the insulin growth factor 1 receptor (IGF-1) compared to human insulin and an eight-fold increased mitogenic potency compared to human insulin in *in vitro* studies. The safety implications of this increased growth-stimulating potential of insulin glargine are unknown and therefore long-term safety data will be essential.

The observation of a three-grade progression of retinopathy in some patients with type 2 DM treated with insulin glargine in studies of 1 year or less has also raised safety concerns, although an independent panel concluded that the progression was not related to therapy with insulin glargine.

**Recent studies**

More recent studies presented as abstract form alone have provided further data on the potential of insulin glargine. The combination use of insulin glargine and insulin lispro was compared with the combination of isophane insulin and insulin lispro in 121 patients with type 1 DM over a 1-year period. There were significantly fewer episodes of both symptomatic and nocturnal hypoglycaemia in the glargine group, but a significant reduction in glycaemic control in the glargine group compared to the isophane group. Other workers have found that the combination of insulin glargine and lispro is superior to the combination of isophane insulin and regular insulin in type 1 DM in terms of frequency of nocturnal hypoglycaemia, but with equivalent glycaemic control. Two studies have reported a lower frequency of nocturnal hypoglycaemia in patients with type 2 DM using the combination of insulin glargine and oral therapy compared to the combination of isophane insulin and oral therapy.

**Summary of trial results**

Insulin glargine has a longer duration and a flat release profile compared to isophane insulin. It has shown to be equivalent in efficacy compared to isophane insulin in patients with both type 1 and 2 DM in terms of glycaemic control as measured by a reduction of HbA1c. Some studies have demonstrated lower fasting plasma glucose in patients treated with insulin glargine compared to conventional isophane insulin despite similar HbA1c values, the significance of which is not fully understood, but which is likely to be beneficial. Some workers have demonstrated a significantly lower incidence of nocturnal and symptomatic hypoglycaemia in patients using insulin glargine compared to isophane insulin. Others found no significant difference in the incidence of symptomatic hypoglycaemia and nocturnal hypoglycaemia. A higher incidence of nocturnal hypoglycaemia in patients using insulin glargine compared to isophane insulin was reported in one study.

**Further studies**

Disappointingly, the use of insulin glargine has not demonstrated better overall glycaemic control compared to isophane insulin, despite insulin glargine being associated with a lower risk of hypoglycaemia in most published studies. The designs of the early clinical trials may have limited the potential usefulness of insulin glargine, with dose-titration of the pre-meal insulins being inadequate or infrequent. However, the potential for a lower incidence of nocturnal hypoglycaemia is likely to be of significant clinical importance. Further studies are required to fully assess the usefulness of insulin glargine, particularly the combination of insulin glargine with fast-acting insulin analogues. In addition, further work on the cost-effectiveness and quality-of-life effects of insulin glargine are needed, to assess the usefulness of this new product compared to existing basal insulins.

**References**


