

INSULIN ANALOGUES

REVISITED

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Insulin analogues provide additional flexibility in dosing and have overcome some of the disadvantages of traditional insulins in the treatment of diabetes. This article reviews the analogues that are currently available and those in development

The aim of treatment regimens for people with type 1 and type 2 diabetes mellitus is to maintain effective glycaemic and blood pressure control in order to avoid the development of microvascular (eg, retinopathy, nephropathy and neuropathy) and macrovascular (eg, coronary heart disease, cerebrovascular disease and peripheral vascular disease) complications.^{1,2} People with type 1 diabetes have little or no endogenous insulin secretory capacity and therefore require insulin therapy for survival. Ideally, insulin regimens should mimic as closely as possible the insulin profile of healthy individuals: that is, post-prandial spikes and basal (low-level background) insulin levels. In many people with type 2 diabetes, glycaemic control can be achieved by a combination of diet and increased physical activity, or diet and exercise together with the use of oral antidiabetic drugs (OADs). However, people with type 2 diabetes who cannot be adequately controlled by oral therapy and diet require insulin treatment either in addition to or in place of OADs.

Advances in insulin technology have revolutionised the treatment of diabetes, and therapy has become increasingly sophisticated to the point where insulin regimens can be specifically tailored to individual need. Key to the improvement in insulin therapy has been the advent of recombinant DNA technology which enabled the synthesis of insulin analogues, thus providing additional flexibility in dosing and overcoming some of the disadvantages of currently available insulin preparations.

The purpose of this review is to provide an overview of the insulin analogues available today and those in development, and to detail their particular benefits.

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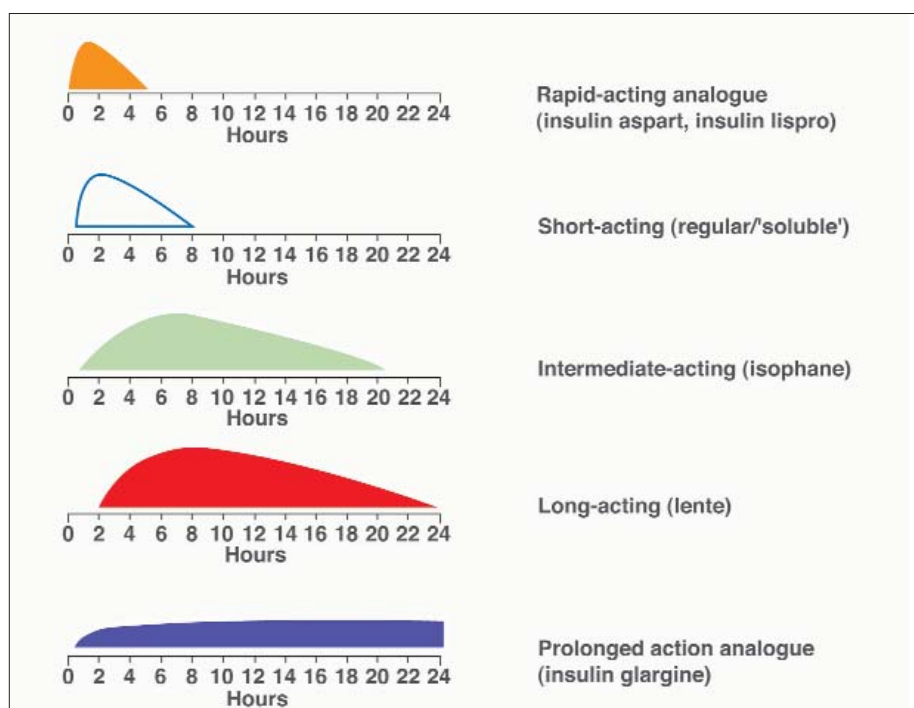


Figure 1: Schematic diagram showing the approximate onset and duration of action of insulin preparations. (Adapted with permission from RSM Press Ltd⁴)

USE OF INSULIN

Insulin was first used to treat people with diabetes in the 1920s. Until the 1980s, advances in insulin therapy were confined to improving methods of the purification and preparation of animal insulin to enhance its pharmacokinetic profile.³ In order to mimic the basal insulin supply of healthy individuals, such modifications to the preparation of insulin have focused on extending the duration of action. Varying the particle size of insulin can alter its absorption characteristics. Delayed action insulins include isophane (neutral protamine Hagedorn [NPH]), lente and ultralente insulin. Iso-phane insulin preparations contain equal concentrations of insulin, zinc ions and protamine (highly basic protein) that cause insulin to crystallise at a neutral pH. Iso-phane insulin was developed by Hagedorn

and colleagues in 1946 and has a duration of action of eight to 14 hours (Figure 1⁴).³ Lente and ultralente preparations have a duration of action of 10–24 hours and 12–28 hours, respectively.⁵ These are amorphous or crystalline precipitates containing only a defined amount of zinc.

In contrast, soluble (regular) insulin has a short onset (0.5–1 hour), early peak (two to five hours), and short duration (six to eight hours) of action, and is, therefore, suitable for use at meal times (Figure 1). The combination of a prandial insulin and a basal insulin supply is known as a basal-bolus regimen.

Despite modifications in the absorption characteristics and pharmacokinetic properties of insulin, these treatments still do not provide optimal timing of insulin action. For example, soluble insulin used for post-prandial glucose control does not have a fast enough onset of action and has an inappro-

which give a reliable measure of blood glucose concentrations over the previous two to three months, were also lower in those treated with insulin lispro for 12 months (8.1 per cent vs 8.3 per cent, $P < 0.05$).^{14,15} In addition, the rate of hypoglycaemia was 12 per cent lower in patients treated with insulin lispro than in patients treated with human soluble insulin (6.4 ± 0.2 vs 7.2 ± 0.3 episodes/30 days, $P < 0.001$).¹⁴

In people with type 2 diabetes, the rise in post-prandial serum glucose levels in response to insulin lispro compared with human soluble insulin was 30 per cent lower (2.6 ± 0.1 mmol/L vs 3.7 ± 0.1 mmol/L) after one hour and 53 per cent lower (1.4 ± 0.1 mmol/L vs 3.0 ± 0.1 mmol/L) after two hours. Insulin lispro treatment was also associated with fewer asymptomatic hypoglycaemic episodes in these people.¹⁶ Similarly, in people with type 1 diabetes, significantly fewer severe hypoglycaemic events were observed in the insulin lispro-treated group than in people treated with human soluble insulin (36 vs 58, $P < 0.05$). These included fewer reports of coma (3 vs 16, $P < 0.005$) and nocturnal hypoglycaemia (176 vs 312, $P < 0.001$).^{9,17} Furthermore, a large, multinational, quality of life study involving people with type 1 diabetes using either insulin lispro or human soluble insulin demonstrated that treatment satisfaction scores ($P < 0.001$) and treatment flexibility scores ($P = 0.001$) were higher for insulin lispro.¹⁸

In a major diabetes centre, it was observed that HbA_{1c} levels decreased but the number of severe hypoglycaemic events increased after the release of a report in 1993 from the Diabetes Control and Complications Trial,² which recommended intensive insulin therapy (multiple daily insulin injections). After the introduction of insulin lispro in 1996, HbA_{1c} levels decreased again, but the increase in incidence of severe hypoglycaemic episodes occurring after the DCCT results did not occur with insulin lispro use.¹⁹

Administration — Insulin lispro should be injected subcutaneously 15 minutes before, or immediately after, a meal.

Insulin aspart Insulin aspart (NovoRapid) differs from soluble insulin by the replacement of a proline at position B28 with a negatively charged aspartic acid (Figure 3). This modification causes a faster dissociation of insulin aspart from hexamers into monomers and dimers, allowing a more rapid absorption from subcutaneous tissue when compared with soluble insulin.²⁰ In healthy volunteers, insulin aspart has an onset of action of 10 to 20 minutes, reaches maximum serum concentrations in 45 minutes and has a duration of action of between one and three hours.^{21–23}

Insulin aspart is also associated with a reduced number of blood glucose excursions

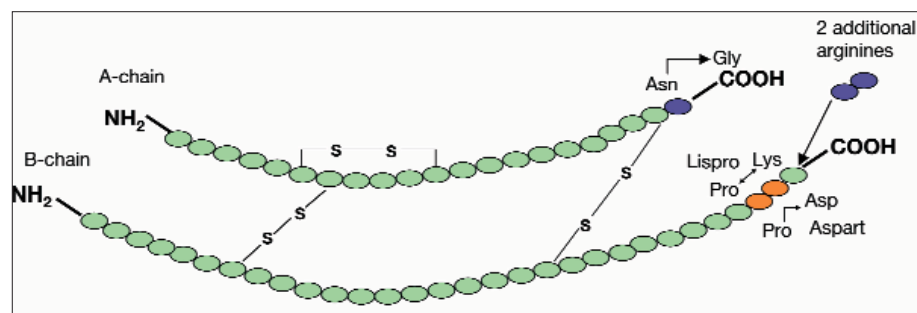


Figure 3: Schematic diagram of the insulin molecule with the modifications of insulin analogues indicated. Insulin glargine has a glycine substituted for an asparagine at position 21 of the A chain, and two arginine residues added to the B chain. Insulin lispro has a proline and lysine at positions 28 and 29 of the B chain switched around. Insulin aspart has a proline substituted for an aspartic acid at position 28 of the B chain

outside a predefined normal range (4.0 – 7.0 mmol/L) compared with human soluble insulin.^{23,24} In a glucose clamp study in healthy volunteers, the intra- and inter-individual variability in absorption of insulin aspart was much lower than that of human soluble insulin.²⁵ In a six-month study in 822 people with type 1 diabetes, significant improvements in glycaemic control, as measured by decreases in post-prandial blood glucose levels and HbA_{1c} levels, were observed in the group treated with insulin aspart compared with human soluble insulin.²⁶ This improvement in glycaemic control with insulin aspart treatment has also been associated with a lower incidence of severe hypoglycaemic events requiring external assistance.²⁴

A comparative study of insulin lispro and insulin aspart in 14 people with type 1 diabetes showed that the two insulins have a similar free plasma insulin profile; however, insulin lispro had a slightly faster onset of action and a faster decline.²⁷

Administration — Insulin aspart is injected subcutaneously immediately before a meal. The individual requirement is usually 0.5 – 1.0 units/kg/day. In a meal-related treatment, 50 – 70 per cent of this insulin requirement may be provided by insulin aspart and the remainder by intermediate- or long-acting insulin.²⁸

LONG-ACTING ANALOGUES

An ideal basal insulin would have a long duration of action — providing 24-hour control with minimal variability in absorption — and preferably could be administered once daily. Traditionally available intermediate- and long-acting insulins, such as isophane insulin, lente and ultralente, are unsatisfactory basal insulins for several reasons.

Isophane insulin has a peak of action four to six hours after injection, followed by a waning of activity. Therefore, when it is administered at bedtime, insulin levels peak between midnight and 2am, when less insulin is required, potentially causing nocturnal hypoglycaemia.²⁹ Nocturnal hypoglycaemia

occurs in 30 to 40 per cent of patients, and is of particular concern with respect to basal insulin therapy.⁴ Furthermore, the duration of action of the intermediate-acting preparations, such as isophane insulin, is not sufficiently long enough to cover the greater insulin requirements at dawn.³⁰

Although ultralente has a long duration of action (12 to 28 hours), a major disadvantage of its use is the high degree of variability among patients in their response after subcutaneous injection. In addition, accumulation leads to a steady state after several days of treatment, which prevents flexible dose adjustment according to the patient's changing needs.³¹

The development of long-acting basal insulin analogues is based on two approaches: changing the insulin pH to neutral, causing it to precipitate in the subcutaneous tissue and thus delaying its absorption; or binding insulin to a serum carrier with a prolonged half-life to delay its activity. Insulin glargine is the only currently available long-acting insulin analogue, although detemir, another long-acting analogue, is currently being developed.

Insulin glargine Insulin glargine (Lantus) is currently the only true long-acting basal human insulin on the market. It is effective when used once daily.³² It was designed to have a long duration of action and no pronounced peak of activity. This was achieved by substituting an asparagine residue with a glycine at position 21 of the A-chain, and elongating the B-chain at the C-terminus by the addition of two arginine residues (Figure 3).³³ The B-chain modification causes the point of least solubility to shift from pH 5.4 to 6.7, making insulin glargine less soluble at the physiological pH of subcutaneous tissue. The glycine substitution of the A-chain of insulin glargine stabilises inter-hexamer interactions, contributing to its delayed delivery from the subcutaneous depot, and maintaining its stability in the acidic solutions in which it must be formulated. Formulating insulin glargine as an acidic, clear solution means that it does not require mixing before administration, there-

Panel 1: NICE guidance on long-acting insulin analogues

The National Institute for Clinical Excellence (NICE) issued the following guidance on use of insulin glargine (the only marketed long-acting analogue) in December 2002:

- (1) Insulin glargine is recommended as a treatment option for people with type 1 diabetes
 (2) Insulin glargine is not recommended for routine use for people with type 2 diabetes who require insulin therapy. Insulin glargine treatment should be considered only for those people with type 2 diabetes who require insulin therapy and who fall into one of the following categories:
- those who require assistance from a carer or healthcare professional to administer their insulin injections
 - those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes
 - those who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs

by reducing the variability seen with insoluble preparations that require mixing, such as isophane insulin.³⁴ (Because of the formulation, insulin glargine must not be mixed with any other insulin or solution as it may become cloudy, possibly resulting in the alteration of its pharmacokinetic or pharmacodynamic profile.) Insulin glargine precipitates at physiological pH and is absorbed slowly from the injection site, thereby potentially providing the first true basal insulin that mimics the insulin profile of healthy individuals.

Insulin glargine has been shown to be absorbed significantly less rapidly than isophane insulin in both healthy volunteers³⁵ and people with type 2 diabetes (T_{75} [time taken for 75 per cent of labelled insulin to disappear from the injection site] 15.0 vs 6.5 hours, $P<0.01$).³⁶ In addition, glucose clamp studies in healthy volunteers and people with type 1 diabetes have demonstrated that the time-action profile of insulin glargine is smoother than isophane insulin with the same onset of action. Insulin glargine did not have the pronounced peak of metabolic activity seen with isophane insulin, and exhibited a more prolonged activity than both isophane insulin and ultralente.^{34,37}

The National Institute for Clinical Excellence issued guidance on the use of insulin glargine in December 2002 (see Panel 1).

Studies with insulin glargine in people with type 1 diabetes Numerous studies have demonstrated the efficacy and safety of insulin glargine in people with type 1 diabetes, particularly with respect to a lowered incidence of nocturnal hypoglycaemia. In a 28-week study involving 534 patients, significantly greater reductions in fasting blood glucose (FBG) levels from baseline were observed in people with diabetes treated with insulin glargine compared with isophane insulin. More people in the insulin glargine-treated group reached the target capillary FBG value of <6.7 mmol/L by the end of the

study (28.3 per cent vs 24 per cent). Furthermore, fewer people treated with insulin glargine, compared with people treated with isophane insulin, experienced symptomatic hypoglycaemia (39.9 per cent vs 49.2 per cent, $P<0.05$) or nocturnal hypoglycaemia (18.2 per cent vs 27.1 per cent, $P<0.05$).³² Similar results were observed in people treated with a combination of insulin glargine and insulin lispro as part of a basal-bolus therapy, compared with isophane insulin.³²

Fewer people treated with insulin glargine experienced nocturnal hypoglycaemia (36 per cent vs 55 per cent, $P<0.005$) compared with people receiving isophane insulin once daily.³⁸ Longer-term studies comparing the effects of insulin glargine and isophane insulin on HbA_{1c} levels are awaited with interest. The efficacy and safety of insulin in children and adolescents has also been demonstrated.^{39,40} In this patient population, blood glucose levels showed minimal glucose excursion over 24 hours and remained stable during the night; also, greater decreases in FBG were observed in insulin glargine-treated patients than those treated with isophane insulin. In addition, less frequent severe, nocturnal or severe nocturnal hypoglycaemia was observed in insulin glargine-treated patients compared with those treated with isophane insulin.^{39,40}

Use of insulin glargine by people with type 1 diabetes was associated with greater treatment satisfaction compared with those who received isophane.⁴¹ Treatment satisfaction improved at all time points analysed; in addition, there was an increased wish to continue treatment in the insulin glargine group, compared with a decrease in the isophane insulin group.

Studies with insulin glargine in people with type 2 diabetes Diet and exercise therapy, followed by the administration of OADs, is the preferred method of therapy in people with type 2 diabetes. Over time, however, people with type 2 diabetes will experience declining beta-cell function and may require insulin therapy. Insulin glargine

has been shown to provide effective glycaemic control and is well tolerated in people with type 2 diabetes.⁴²⁻⁴⁴ In a study of people with type 2 diabetes who were not receiving OADs and who had previously received basal insulin, insulin glargine and isophane insulin provided equivalent levels of glycaemic control, but the incidence of nocturnal hypoglycaemia was reduced by 25 per cent in the insulin glargine group. In addition, people with diabetes treated with insulin glargine gained less weight.^{43,44} These studies support the earlier use of insulin glargine in the management of type 2 diabetes to meet the tighter glycaemic targets set by the International Diabetes Federation.⁴⁵

A 12-month trial that assessed satisfaction and well-being in people with type 2 diabetes reported a more pronounced increase in patient satisfaction for insulin glargine than isophane insulin treatment, especially in the latter half of the study.⁴⁶ This study

indicates that people with diabetes using insulin glargine have an improved quality of life.

Administration — Insulin glargine is injected subcutaneously once daily at bedtime; it is initiated at an average dose of 10 units once daily, and is subsequently adjusted, according to the patient's need, to a total daily dose ranging from 2–100 units.⁴⁷ If the patient is switching to insulin glargine, there is no need to alter the initial dose if the previous regimen was a once-daily dose of human isophane insulin or human ultralente insulin. However, if the previous regimen was a twice-daily dose of isophane insulin, the initial dose of insulin glargine is usually reduced by 20 per cent compared with the total daily isophane insulin dose in the first week of treatment to avoid hypoglycaemia. The dose of insulin glargine can then be adjusted based on the patient's response.⁴⁷

Insulin detemir Modifying insulin to promote the binding of serum proteins, such as albumin, has been hypothesised to prolong its duration of action. Insulin detemir (Lys^{B29}[N^ε-tetradecanoyl] des[B30] human insulin) is a soluble basal insulin analogue. It is acetylated with a 14 carbon fatty acid chain, which causes it to bind reversibly to albumin in plasma.⁴⁸ Only free insulin detemir is biologically active, and its slow dissociation from albumin results in delayed action.⁴⁹

Euglycaemic clamp studies in dogs demonstrated the equivalent steady-state action of equimolar physiological infusions of soluble insulin and detemir.⁴⁹ Pharmacokinetic and pharmacodynamic studies in healthy volunteers showed that the metabolic response — as measured by glucose infusion rates — was slower and did not have a pronounced peak in response to insulin detemir, unlike isophane insulin.⁵⁰ There was no dose-dependent effect of insulin detemir on

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glucose infusion rates, and the duration of action was not different from that for isophane insulin.⁵⁰

A multicentre, open, randomised study of 59 patients with type 1 diabetes showed that insulin detemir was as effective as isophane insulin in maintaining glycaemic control, but was associated with less intra-subject variation in fasting blood glucose levels, and had a delayed onset of action. People treated with insulin detemir experienced fewer episodes of hypoglycaemia, but only in the last week of the six-week trial.⁵¹ However, 64 per cent of people on insulin detemir needed to be administered a dose that was large enough to require two injections, which were given concurrently. The mean dose for insulin detemir was 2.4 times greater than for isophane. Another study showed that insulin detemir provided similar glycaemic control and was associated with a similar incidence of hypoglycaemia compared with isophane insulin but was administered twice daily.⁵²

Hepatospecific insulin analogues

Ideally, exogenous insulin would be delivered into the hepatic portal vein to mimic insulin action in normal individuals; this is not currently possible with subcutaneous insulin delivery. Development of novel insulin analogues that are targeted specifically to the liver offers another alternative to intraperitoneal insulin pumps, pancreatic transplantation or islet cell transplantation. Na^aB¹L-thyroxyl-insulin (B1-T4-insulin) has been engineered to bind, via a hydroxyl moiety, to thyroid hormone-binding proteins in the plasma to form high molecular weight complexes. This is thought to confer relative hepatoselectivity by inhibiting trans-capillary access to peripheral tissues.⁵³ A pilot study showed that this insulin analogue had a similar duration of action to isophane insulin, as determined by the maintenance of euglycaemia and the effect on hepatic glucose production. In contrast, less effect on

peripheral glucose uptake was observed in response to B1-T4-insulin compared with isophane insulin. A peak of action at six hours was observed in response to B1-T4-insulin and isophane insulin.⁵⁴

CONCLUSIONS

The development of new insulin analogues has allowed the basal-bolus regimen of insulin therapy to be dramatically improved. Greater flexibility in patient lifestyle has been achieved by the fast-acting insulin analogues such as insulin lispro and insulin aspart that can be injected immediately before meals.

The traditional basal insulins have been less than ideal because they do not have a long duration of action and, more importantly, they have inappropriate peaks of action that can cause nocturnal hypoglycaemia.

The flexibility of recombinant DNA technology has facilitated the development

of novel modifications to insulin that can change the duration and action, and help to prevent the occurrence of episodes of nocturnal hypoglycaemia. Insulin glargine is the first true basal insulin because it has been modified such that the duration of action is longer (approximately 24 hours) and the profile of action smoother, when compared with other forms of insulin. Clinical trials in people with type 1 and type 2 diabetes have shown that, with once-daily use, it provides at least equivalent glycaemic control to isophane insulin (one of the most widely used intermediate-acting insulin formulations), but is associated with a decreased incidence of hypoglycaemia and less weight gain. The available data for insulin detemir also seem positive, although more information is needed before the clinical efficacy of this insulin can be properly assessed.

The development of long-acting insulin analogues such as insulin glargine and insulin detemir is especially encouraging for people with type 2 diabetes who are not adequately controlled by OADs. Continued progress in the field of insulin analogues should result in significant improvements in treatment options for all people with diabetes.

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