

# An update on insulin analogues

Recombinant DNA technology has enabled the production of insulin analogues. In this article, Irene Gummerson discusses the products and their benefits over standard formulations

An insulin analogue is an insulin molecule whose composition has been altered in order to yield some advantage over standard human insulin, while retaining its biological effect. In the 1990s, insulin lispro (Humalog) was the first analogue to be licensed in the UK. Insulin glulisine is the latest.

People with type 1 diabetes have no endogenous insulin secretory capacity and, require insulin therapy for survival. Ideally, the insulin regimens used should mimic the 24-hour insulin profile of non-diabetic individuals: post prandial spikes and basal (low-level background) levels, preventing hyperglycaemia without inducing hypoglycaemia.

In type 2 diabetes, glycaemic control can be achieved by a combination of diet and increased physical activity, with or without oral antidiabetic drugs (OADs). However, where the diabetes cannot be adequately controlled in this way, insulin therapy should be considered, either in addition to, or in place of OADs.

Chronic hyperglycaemia is associated with increased microvascular complications. Intensive insulin treatment can result in near normoglycaemia and so reduce the likelihood or severity of such complications. However using standard (non-analogue) human insulin formulations to achieve such diabetic control is, in some patients, limited by the increased likelihood of severe hypoglycaemia (see below), which is a significant cause of morbidity. Nocturnal hypoglycaemic episodes can be a particular problem.

## Short-acting insulins

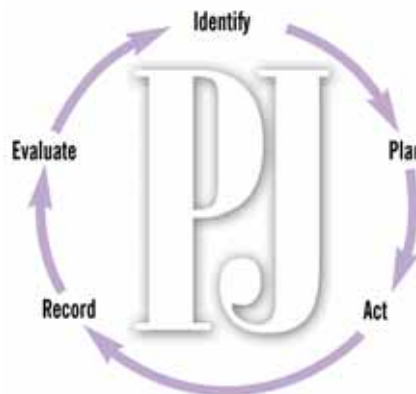
Short-acting (soluble, non-analogue) standard insulins cover the patient's requirements for insulin at mealtimes. The solution is clear, and contains an equilibrium mixture of monomers, dimers, hexamers etc. After subcutaneous (sc) injection, the rate of absorption is determined largely by how quickly the polymers dissociate into monomers, which are then rapidly absorbed at the injection site.

It is this rate of dissociation (30 minutes or more) that delays entry of free insulin into the circulation, producing a lower peak in the early phase of glucose absorption after a meal. Insulin levels fall slowly after the peak, with the risk of hypoglycaemia later. The influence of short-acting insulin on post-prandial hyperglycaemia is improved by sc administration 30 minutes or more before eating, but this is something patients find difficulty keeping to. Chronic post-prandial hyperglycaemia can increase a HbA1c level (an indicator of glycaemic control in the past two to three months) and may be linked to increased cardiovascular disease.



Sanofi-aventis

Insulin glulisine is the latest analogue in the UK



## Identify knowledge gaps

1. Can you list all the categories of insulin?
2. What are the benefits of insulin analogues over standard formulations?
3. Which analogues can be used in insulin pumps?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: [www.rpsgb.org/education](http://www.rpsgb.org/education)). This article relates to "common disease states and their drug therapies".

**Rapid-acting insulin analogues** (See Table 1, p172.) Monomeric insulins are absorbed two to three times faster than standard soluble insulin. Three are available in the UK:

- Aspart
- Lispro
- Glulisine

Since these act without the delay that otherwise would occur, they can be injected shortly before, or just after a meal. The amino acid changes that have been made to each formulation result in a more weakly associated hexamer, the rapid dissociation of which results in a corresponding rapid onset and peak as well as shorter duration of action, compared with standard soluble insulin. This should result in better post-prandial control and less hypoglycaemia. It should be noted, however, that patients whose blood glucose has greatly improved may experience a change in their symptoms of hypoglycaemia. If hypoglycaemia occurs, it may occur sooner after an injection compared with soluble human insulin.

Compared with standard soluble insulin, rapid-acting insulin analogues may produce a modest but significant reduction in HbA1c when used in continuous sc insulin infusions (CSII, or insulin pump), and are said to be preferred by patients.

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## Panel 1: NICE guidance on insulin glargine

Insulin glargine can be used as a treatment option for people with type 1 diabetes. For people with type 2 diabetes who require insulin therapy, it should only be considered for those:

- Requiring assistance from a carer or healthcare professional to administer their insulin injections
- Whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes
- Who would otherwise need twice-daily basal injections in combination with OADs

**Insulin lispro** Insulin lispro (Humalog) can be given in conjunction with longer-acting human insulins or sulphonylureas, or by CSII, and may be given intravenously (eg, for control of blood glucose levels during ketoacidosis).

**Insulin aspart** Insulin aspart (NovoRapid) should normally be used in combination with an intermediate- or long-acting insulin given at least once a day; or by CSII pump. When used in an insulin pump, NovoRapid should not be mixed with any other insulin due to the absence of compatibility studies.

**Insulin glulisine** Insulin glulisine (Apidra) should be used in regimens that include an intermediate- or long-acting insulin or basal insulin analogue and can be used with OADs. Apidra should be given by sc injection or CSII but must not be mixed with any formulations other than isophane (NPH; neutral protamine Hagedorn) insulin. When used with an insulin pump, Apidra must not be mixed with diluents or other insulin. Apidra should not be used in children or adolescents — the summary of product characteristics states that there is no adequate clinical information on its use in these groups.

### Biphasic insulin analogues

(See Table 2, p172.) Pre-mixed biphasic formulations provide a combination of a faster-acting, shorter-duration analogue with a longer-acting analogue, for dosing before or after meals. The former deals with food being eaten, and the latter maintains background insulin levels.

Once insulin aspart or lispro are co-crystallised with protamine, their absorption is slowed to a similar rate as to that of intermediate-acting standard insulin, isophane insulin.

NovoMix 30 is a biphasic formulation of 30 per cent insulin aspart and 70 per cent protamine-crystallised insulin aspart. In type 2 diabetes, NovoMix 30 can be given in monotherapy or in combination with metformin, when the blood glucose is inadequately controlled with metformin alone. The individual insulin requirement is usually 0.5–1.0 units/kg/day and this may be fully or partially supplied with NovoMix 30. The recommended starting dose of NovoMix 30 in combination with metformin is 0.2 units/kg/day.

Pre-mixed formulations of insulin lispro, Humalog Mix25 and Humalog Mix50, consist

of a mixture of 25 per cent or 50 per cent insulin lispro and 75 per cent or 50 per cent of protamine suspension of insulin lispro, respectively.

NovoMix 30 and Humalog Mix 25 or Mix 50 should never be administered intravenously.

### Longer-acting standard insulins

An ideal basal insulin would provide 24-hour control with minimal variability in absorption, and preferably could be administered once daily.

Standard available intermediate-acting (isophane) and long-acting (lente), are not ideal basal insulins, due to peaks of action, variability of patient response and the risk of suboptimal mixing. Isophane insulin has a peak of action approximately 5 to 7 hours after injection, followed by a waning of activity. Therefore, when isophane insulin is administered at bedtime, insulin levels may peak during the early hours, when less insulin is required, potentially causing nocturnal hypoglycaemia. The duration of action of isophane, may not be long enough to cover the insulin requirements at dawn.

Although insulin lente has a long duration of action (up to 24 hours), a disadvantage of its use is a degree of variability between patients in their responses after sc injection. Suboptimal mixing of the insulin suspension could also be a cause of intra-patient variation in response to the same dose.

**Long-acting analogue insulins** (See Table 3, p172.) The development of long-acting basal insulin analogues is based on two approaches: changing the isoelectric point (the pH at which insulin is least soluble, and precipitates) or binding insulin to a serum albumin carrier via a fatty acid side chain.

Insulin glargine (Lantus) uses the first approach. Changing the isoelectric point results in an insulin molecule that is soluble at acidic pH, but which precipitates in sc tissues where the pH is near neutral. Small amounts of insulin glargine can then gradually go back into solution, giving a relatively flat insulin profile and a duration close to 24 hours.

Lantus is approved for use once daily, at the same time each day. Due to a more sustained basal insulin supply, less nocturnal but more early-morning hypoglycaemia can be expected. Because of its acidic pH, insulin glargine cannot be mixed with any other insulin preparation and it must be injected separately, and at least a few centimetres away, from any other insulin being injected at the same time. Mixing or diluting can change its time-action profile and also cause precipitation. It is important to ensure that syringes do not contain traces of any other material, and also that insulin glargine is clear and not cloudy. NICE issued guidance on long-acting insulin analogues in 2002 (see Panel 1).

In children, the efficacy and safety of Lantus have only been demonstrated when given in the evening, but it is not licensed for children under the age of six years.

The development of the fast-acting insulin analogues has allowed a greater flexibility in patient lifestyle

Insulin detemir (Levemir) uses the second approach. The action of insulin detemir is prolonged (up to 24 hours, depending on the dose provided) and this is mediated by the strong self-association of insulin detemir hexamers at the injection site, and albumin binding via the fatty acid side-chain. These combined mechanisms of protraction provide a more reproducible absorption and action profile of insulin detemir compared with isophane insulin. Distribution to peripheral target tissues is slower compared with isophane insulin.

Levemir is licensed for the treatment of diabetes, to be administered sc once or twice a day, in combination with meal-related short- or rapid-acting insulin. For people who require twice daily dosing to optimise blood glucose control, the second dose of the day, can be given in the evening or at bedtime.

Intravenous administration of the usual sc dose of either insulin detemir or glargine could result in severe hypoglycaemia, and should be avoided. Neither, should be the insulin of choice for the treatment of diabetic ketoacidosis. Instead, standard soluble insulin administered intravenously, is recommended in such cases.

## Discussion

The aim of therapy in type 1 and type 2 diabetes is to reach if possible, the currently recommended glycaemic targets, with the ultimate goal of preventing the onset or worsening of microvascular complications, without hypoglycaemia seriously impacting on the quality of life.

Compared with the use of standard human insulin, the use of the fast-acting analogues is associated with a modest decrease in HbA1c levels in people with type 1, but not type 2 diabetes. Use of an analogue does not reduce the overall frequency of hypoglycaemia compared with standard human insulin, either in people with type 1 or type 2 diabetes, but the incidence of severe hypoglycaemic episodes appear fewer. One comment from a diabetes specialist nurse was: "Not experiencing the extreme highs and lows of blood glucose control, increases patients' confidence in being able to adjust their insulin, as it becomes easier to control, and also improves the professionals' confidence to help encourage patients to go for tighter control."

Insulin aspart and lispro have similar effects on HbA1c levels and the incidence of hypoglycaemia to isophane insulin, but they appear to reduce postprandial glucose concentrations more.

When compared with standard soluble insulin, insulin analogues result in a modest but significant reduction in HbA1c when used in insulin pumps, and are preferred by patients. However, there is conflicting evidence as to whether or not there is any significant difference in the number of severe hypoglycaemic attacks, between analogue and soluble insulin when used in the pumps.

The development of the fast-acting insulin analogues has allowed a greater flexibility in



**Insulin glargine is soluble at acidic pH but precipitates in subcutaneous tissues**

patient lifestyle (where patients can inject immediately before, or just after meals), as have the pre-mixed biphasic formulations.

The absorption profile of isophane insulin can vary from injection to injection, partly due to its formulation. To avoid erratic dosing, being a suspension, it needs to be mixed before each administration. For patients, who find isophane insulin suitable, variability between doses may be reduced to some degree by ensuring that patients use the correct mixing method (eg, gently rolling the vial or cartridge between the palms rather than vigorously shaking it), which can be found in patient information leaflets. Further variability can arise after injection, because dissolution of the insulin crystals must take place before absorption into the blood stream can occur, and this may be an unpredictable process. Moreover, blood flow to the injection site can vary.

The basal insulin analogues, insulin glargine and detemir, provide a more predictable basal action than standard longer-acting insulins. They are formulated as solutions, and therefore do not need mixing before injecting. The formation and subsequent re-dissolution of the precipitate after injection of insulin glargine, might explain why some small degree of variability could still occur. Insulin detemir remains soluble after injection. The manufacturer suggests that once insulin detemir is absorbed into the blood stream, reversible albumin binding in plasma may buffer the effect of any change in absorption rate caused by variable blood flow to the injection depot.

In the quest for appropriate blood glucose control, there may be an associated weight gain which may contribute to lower self-esteem. Reduced metabolic rate, the anabolic effects of insulin, the perceived fear of hypoglycaemia and hence defensive eating may contribute to insulin's weight-gaining effect. This may lead increased doses being required and subsequent increased risks of hypoglycaemia. Studies have shown that insulin detemir is associated with a lower weight gain than isophane insulin, in people with type 1 or type 2 diabetes.

Both insulin detemir and insulin glargine result in glycaemic control that is at least comparable that with isophane insulin, as well as appearing to reduce nocturnal hypoglycaemia people with type 1 or type 2 diabetes.

Insulin analogue manufacturers are relentlessly promoting the use of insulin analogues and many clinicians are prescribing them as first-line treatments. The idea of a better physiological absorption profile is attractive, but perhaps prescribers should also consider the possibility of any negative consequences of a change in structure, from that of the natural human insulin molecule. People (especially, those diagnosed with diabetes at a young age) may be injecting these formulations for many decades. To date, no adverse clinical effects that are the result of any differences that these analogues may have in their antigenic or mitogenic properties have been reported compared

## Inhaled insulin

An inhaled rapid-acting insulin preparation has been launched by Pfizer (see p157).

A National Institute for Health and Clinical Excellence technology assessment is expected to be released in October.

**Table 1: Rapid-acting insulin analogues**

Generic name	Available as	Trade name	Manufacturer	Modification	Onset of action (mins)	Maximum duration
Insulin lispro	vial cartridge	Humalog	Eli Lilly	Proline and lysine reversed at B28 and B29	15	Up to 4 hrs
Insulin aspart	vial cartridge pen	NovoRapid	Novo Nordisk	Aspartic acid at B28 instead of proline	10–20	Up to 4 hrs
Insulin glulisine	vial cartridge	Apidra	Sanofi-aventis	Lysine at B3 instead of aspartic acid; glutamic acid at B29 instead of lysine	10–20	Up to 4 hrs

**Table 2: Biphasic insulin analogues**

Generic name	Available as	Trade name	Manufacturer	Modification	Early peak/late peak	Onset of action (mins)	Maximum duration
Insulin lispro	cartridge pen	Humalog Mix 25	Eli Lilly	25% lispro 75% lispro protamine	1–2/4–8 hrs	5–15	10–16 hrs
Insulin lispro	cartridge pen	Humalog Mix 50	Eli Lilly	50% lispro 50% lispro protamine	2–3/4–8 hrs	30–45	10–16 hrs
Insulin aspart	cartridge pen	NovoMix30	Novo Nordisk	30% in soluble phase 70% aspart protamine	1–2/4–8 hrs	5–15	10–16 hrs

**Table 3: Long-acting insulin analogues**

Generic name	Available as	Trade name	Manufacturer	Modification	Maximum duration
Insulin glargine	vial Lantus cartridge* OptiClik cartridge† pen (prefilled)	Lantus	Sanofi-aventis	Glycine at A21; addition of 2 arginines at end of B-chain	20–24 hrs
Insulin detemir	cartridge pen	Levemir	Novo Nordisk	Fatty acid chain attached to B29; B30 threonine removed	20–24 hrs

\* The Lantus cartridge fits into the Optipen Pro  
 † The OptiClik cartridge fits into the OptiClik Pen

with human insulin, but such effects might show up in years to come.

Prescribers should also take into account the cost versus the extra benefit of insulin analogues, compared with standard insulin, and perhaps should not be switching patients from standard therapy to analogues, if they have appropriate glycaemic control without problematic hypoglycaemia.

The insulin analogues currently available provide useful alternatives to standard insulin, especially for people with diabetes who have frequent severe hypoglycaemia or nocturnal hypoglycaemic episodes (predominantly type 1).

It is hoped that developments in the field of insulin analogues will continue to result in significant improvements in treatment options for people with diabetes. The results of well designed, long term trials on the use of these formulations are eagerly awaited.

#### Resources

■ Defronzo RA, Ferrannini E, Keen H, Zimmet P. International textbook of diabetes mellitus. 3rd Ed Vol.1 London: John Wiley & Sons Ltd; 2004.

### Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Familiarise yourself with each product by talking to local nurses, patients and drug company representatives. Make sure you know how each injection device works.
2. Use medicine use reviews to check for problems in patients with diabetes.
3. Find out the details of your local diabetes professionals. Advise within your competency and refer to appropriate professionals when necessary.

### Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities.

Answer the following questions:

What have you learnt?

How has it added value to your practice? (Have you applied this learning or had any feedback?)

What will you do now and how will this be achieved?