Innovative insulins

Where do analogues fit?

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BACKGROUND
Problems with traditional bolus insulins include delayed time to onset and offset, and with basal insulins, an overnight peak and poor reproducibility. Analogue insulins have been formulated to better emulate physiologic insulin secretion and improve glycaemic control without increasing hypoglycaemia.

OBJECTIVE
This article discusses analogue insulins and outlines their role in current diabetes management.

DISCUSSION
Analogue insulins do offer some advantages over traditional insulins. The bolus and basal analogues offer flexibility, and basal analogues reduce nocturnal hypoglycaemia. However, there is limited evidence supporting improved glycaemic control with analogue insulins. No study has looked at long term outcomes and hard endpoints. Rapid acting analogues are widely used, generally in type 1 diabetes. The basal analogues glargine and detemir are significantly more expensive compared to traditional basal insulins, but were listed on the Pharmaceutical Benefits Scheme on 1 October 2006. Glargine is available for patients with type 1 and insulin requiring type 2 diabetes, while detemir has been recommended only for patients with type 1 diabetes. Patients with type 1 diabetes, particularly those with hypoglycaemic unawareness, may be expected to derive most benefit from the new basal analogues.

Insulin therapy was introduced into Australia in 1922, not long after its first use in Canada in 1921. In the 1930s zinc or protamine were added to produce delayed release formulations. Little changed until the 1970s when insulin was purified, and the 1980s when human insulin was produced. In the past 15 years, short and long acting insulin analogues have become available[1,2] and have the potential to improve insulin therapy. In this article we review the available insulin analogues, outline their pros and cons and discuss their use in clinical practice.

Traditional insulins – far from physiologic

Ideally, insulin therapy for diabetes would predictably mimic endogenous insulin secretion. This has proved impossible with traditional basal and bolus insulin preparations. The major differences are the rapid response of insulin secretion to glycaemia, the overnight dip and morning surge of basal insulin secretion, and the portal delivery of insulin from the pancreas. Some of these features can be partly achieved by modern insulin pumps, but responses to glycaemia still rely on blood glucose tests and human intervention. Moreover, insulin is still not delivered portally, which means that the liver is exposed to lower insulin levels than normal, while the systemic levels are higher.

Some idea of how far current formulations are from the ideal can be appreciated in *Figure 1*. Far from the physiologic overnight dip and morning surge, the basal isophane, or neutral protamine Hagedorn (NPH) given at bed time has an overnight peak, while levels fall in the morning. The isophane insulins, based on protamine as the retardant, are now the only traditional basal insulins since the insulin zinc preparations where taken off the market in 2005. The so called 'quick acting' bolus regular insulin has a slow onset, delayed peak and prolonged tail often resulting in hyperglycaemia after a meal and hypoglycaemia before the next.

Patients compensate for these shortcomings in various ways, but while the principle of matching insulin to lifestyle is important, it can be difficult or impossible in practice. Analogue insulins were developed to overcome the limitations of traditional insulin therapy.

Bolus analogues: quicker onset and shorter 'tail'

Following subcutaneous injection, insulin aggregates into dimers and hexamers, which then disassociate into monomers. As insulin is absorbed in its monomeric form,

its onset of action is dependent on this rate of disassociation, which in turn depends on the strength of bonds maintaining the hexameric and dimeric forms. In bolus analogues, the amino acid sequence has been modified to reduce the affinity between insulin molecules, thus speeding disassociation and absorption after injection.

There are three bolus analogue insulins, however glulisine is not available in Australia. The pharmacokinetics and dynamics are much the same for all analogues: onset of action within 5–15 minutes, peak at 30–90 minutes and duration of 4–6 hours (*Table 1*). Compared to regular insulin, they reach twice the peak in half the time and have half the tail[3] (*Figure 2*). In theory they are better bolus insulins, but in practice there are pros and cons. The major advantage to patients is their flexibility. Rather than inject and wait 30–45 minutes before eating to compensate for the delay in absorption of regular insulin, patients can 'inject and eat'. Or 'eat and inject' in the case of parents with young children who may inject, but then not eat, resulting in hypoglycaemia. The flexibility of analogue insulins is attractive to those with an erratic lifestyle who may not be able to predict when, where, and how much they will eat. For those in whom the 'tail' of regular insulin causes late postprandial hypoglycaemia, bolus analogues mean that patients no longer need to compensate for the limitations of the regular insulins by eating unwanted snacks between meals. The rapid onset and offset also mean that corrective doses of insulin control glycaemia quickly and that repeated corrective doses do not accumulate and increase hypoglycaemia.

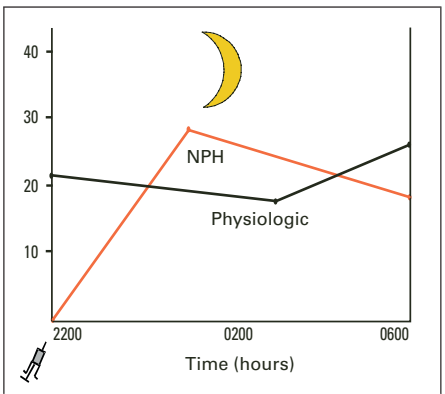


Figure 1. Insulin profile at night

However, the speed of onset and offset also has cons as well as pros. There is a risk of hypoglycaemia if inadequate carbohydrate is eaten, and patients may notice a 'wearing off' between meals with hyperglycaemia before the next meal. It is important that patients understand that they can 'inject and eat', and may no longer be obliged to eat between meal snacks, but that they should include adequate carbohydrate in their meals and be aware that a long gap between meals may cause hyperglycaemia before the next meal.

In clinical trials, the theoretical advantages of bolus analogues over regular insulin have not been clearly demonstrated. A recent Cochrane review[4] found modest improvements of A1c (0.1% for injected and 0.2% for insulin pump therapy in type 1 diabetes, with no effect in type 2 diabetes). There was no difference in overall hypoglycaemia. Another meta-analysis showed a 25% reduction in severe hypoglycaemia with bolus analogues compared to regular insulin in type 1 diabetes.[5] Quality of life was improved in one open label study in type 1 diabetes but this was not shown in double blind studies in type 1 or type 2 diabetes.[6]

Basal analogues: better but not perfect

The current traditional basal insulin is isophane or NPH (protaphane or humulin NPH). The addition of protamine slows absorption and gives the preparation its cloudy appearance. As noted, the pharmacokinetics do not match a physiologic profile, with an overnight peak and waning effect in the morning. In practice, there is also considerable within and between patient variability in the profile and duration of effect, in part due to variable re-suspension of the protamine by the patient. Finally, NPH often requires twice daily dosing to maintain adequate basal insulin levels.

The basal analogues address some of these limitations – they have a flatter profile and no overnight peak, they are more consistently absorbed and once daily dosing often produces adequate basal insulin. However, the analogues still lack the overnight dip and morning surge of the natural insulin profile and are still administered systemically.

The two basal analogues have similar profiles (*Table 2*) but differ in the mechanism of extension of their effect.[1,2] An amino acid substitution makes glargine soluble at the acidic pH of its formulation but insoluble at physiological pH. Injected glargine therefore precipitates in the subcutaneous tissues and crystals slowly dissolve, releasing the modified insulin for absorption. Detemir substitutes a fatty acid for an amino acid. When injected the analogue becomes monomeric, the fatty acid then associates and disassociates first with albumin at the subcutaneous site of injection, then with the albumin in the circulation, and finally with the albumin in the extracellular tissue at the organs of action. This successive association and disassociation further prolongs its action.

The major advantage of the basal analogues is their more reproducible profile compared to isophane. Once daily dosing is an added bonus, although in some cases isophane can be used once daily and in others twice daily dosing is needed for the analogues (detemir is marketed

Table 1. Traditional versus analogue bolus insulin

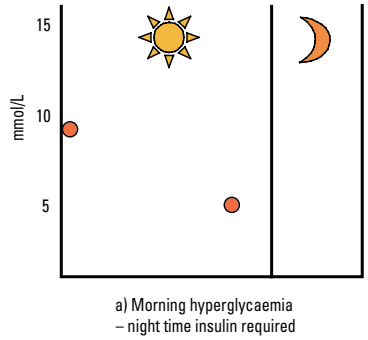
Insulin	Onset	Peak	Duration	Modification	Cost $/100u*
Regular (Actrapid, Humulin R)	30–60 minutes	2–3 hours	8–10 hours	N/A	2.65–2.97
Lispro (Humalog)	5–15 minutes	30–90 minutes	4–6 hours	Substitute lysine for proline at position 28 of the insulin β chain	3.16
Aspart (NovoRapid)	5–15 minutes	30–90 minutes	4–6 hours	Substitute aspartic acid for proline at position 28 of the insulin β chain	3.16–3.51

*Based on PBS dispensed price for maximum quantity (includes dispensing fee and pharmacy mark up)

Table 2. Traditional versus analogue basal insulin

Insulin	Onset	Peak	Duration	Modification	Cost $/100u*
Isophane Neutral protamine Hagedorn (Humulin NPH, protaphane)	2–4 hours	4–10 hours	12–18 hours	N/A	2.65–2.97
Glargine (Lantus)	2–4 hours	N/A	20–24 hours	Substitute glycine for asparagine at position 30 of the insulin β chain	5.75
Detemir (Levemir)	2–4 hours	N/A	20 hours	Threonine is omitted from position 30 of the insulin β chain and replaced by myristic acid, a C14 fatty acid chain which binds to albumin	5.75

*Based on PBS dispensed price for maximum quantity (includes dispensing fee and pharmacy mark up)



a) Morning hyperglycaemia – night time insulin required

Figure 2. Bolus analogues: 1/2Tmax, 2Cmax

as a twice daily insulin and a number of patients require twice daily dosing with glargine). Their flatter profile (so-called 'peakless') results in less nocturnal hypoglycaemia and there is the interesting suggestion that insulin detemir may be associated with weight loss rather than the usual weight gain associated with insulin therapy.

As for the bolus analogues, there are cons as well as pros. Although more expensive that the traditional bolus insulins, both glargine and detemir were listed on the Pharmaceutical Benefits Scheme (PBS) on 1 October 2006. While glargine is approved for patients with both type 1 and type 2 diabetes, detemir is PBS listed only for patients with type 1 diabetes. Both are clear insulins, like the bolus insulins, which may lead to more administration errors than with the traditional basal insulin, which is cloudy and therefore very different from the clear bolus one. Furthermore, currently there is insufficient data to support the mixing of glargine or detemir with bolus insulins. The long duration may also have cons – the same daily dose may result in a gradual accumulation of basal insulin and adjustment may be more difficult. The less frequent administration also means less frequent opportunities to change basal doses and this may make irregular or unplanned activity more difficult to manage.

There have been fewer clinical trials with basal than with bolus insulin analogues. Overall glycaemic control is similar to traditional basal insulins, although some studies have shown a modest improvement (A1c reduction of up to 0.2%).[7,8] Nocturnal hypoglycaemia is reduced in most but not all studies in patients with type 1 and type 2 diabetes.[7,8] Although weight gain usually accompanies improved glycaemic control, some trials have reported modest weight loss with insulin detemir despite improved glycaemic control.[8] There have been no long term trials assessing hard endpoints such as occurrence or progression of diabetes related complications and no head to head trials of glargine and detemir.

Continuous subcutaneous insulin infusions vs. basal-bolus analogues

Continuous subcutaneous insulin infusions (CSII) offer another alternative to basal-bolus treatment for intensive insulin therapy. Continuous subcutaneous insulin infusion is achieved via a subcutaneous catheter, usually inserted into the abdomen, attached to a small external pump. Regular insulin was the first insulin used when pumps were developed over 20 years ago, but due to superior glycaemic control, rapid acting analogues are now generally used for CSII. The basal rate is adjustable, and this enables the difficult nocturnal physiology of insulin secretion to be more closely replicated. Bolus doses are programmed by the user, generally using formulae provided by the pump manufacturers – these take into account pre-prandial blood sugar levels and carbohydrate load. Patients need to be motivated, and significant education and training, including dietetic input for carbohydrate counting, is required.

Before the introduction of basal analogues, CSII therapy was generally shown to offer superior glycaemic control over traditional basal-bolus therapy. However, more recently, basal analogues have been referred to as 'the poor man's pump'. A small number of studies have compared CSII and basal-bolus treatment with long acting analogues in type 1 populations (adults and children) – these demonstrated either equivalence, or a small advantage in favour of CSII therapy.[9] Continuous subcutaneous insulin infusion therapy has offered equivalent glycaemic control to basal-bolus therapy with basal analogues in type 2 diabetes.[10] Rates of hypoglycaemia and weight gain appear to be similar with these therapies. At this stage, cost is a limiting factor. The pumps cost $5000–10 000 and may be covered through private health insurance. The subcutaneous catheters are changed every 3 days, and the insulin lines every 6 days. These consumables are now subsidised, and although previously costing up to $300 per month, now cost around $30 per month.

Safety issues

There are some data on the safety of the use of bolus analogues in pregnancy. Lispro has the best data, all of which is retrospective.[1,11] However, expert opinion suggests lispro can be safely used in pregnancy. Due to lack of data, the basal analogues are rarely used in pregnancy.

Bolus analogues are widely used in the paediatric population, mainly because their flexibility suits the variable lifestyle of the population.[12] There are limited data with the basal analogues in the paediatric population, particularly with the newer basal analogue detemir. The analogue insulins have the potential to make intensive treatment schedules more effective in the paediatric population. However, children and/or their parents may find it difficult to meet the demands of extra monitoring of blood glucose, diet and activity.

There has been some concern about the potential of neoplasia with analogues since the development insulin analogue (ASP B10) was abandoned because of an association with mammary ovarian and bone tumours in animals. Worldwide, millions of people have used the analogues in the past 15 years (more bolus than basal) and there have been no safety concerns to date. Nonetheless, neoplastic potential remains an issue and should be considered, especially with the basal analogues.

As noted there are limited data suggesting that the insulin analogues may produce modest improvements in glycaemic control and reduce the risk of night time and severe hypoglycaemia. There is no evidence to date of adverse effects on short or long term diabetic complications. However, it should be noted that trials generally exclude patients with significant microvascular complications and those with frequent hypoglycaemia or hypoglycaemic unawareness.

Analogues in practice

The major advantages of the insulin analogues are the rapid onset and offset of the bolus analogues, the flatter insulin profile of the basal analogues and the reproducibility of effect for both. The major disadvantage is the cost to the government (and taxpayer) for the more expensive bolus and basal insulins.

Many patients appreciate the flexibility and convenience of analogues but these advantages may not be enough to justify the cost. In the authors' opinion, there are two clear situations in the management of type 1 diabetes where the use of analogues is more easily justified: basal and postprandial glycaemic swings, especially in those with hypoglycaemic unawareness. Two case studies may make this clearer.

Case study 1

'I do the same thing each day. I eat the same, do the same activity, inject the same insulin. One day I will wake up at 5 (mmol/L) – beautiful. The next day I am 15. It drives me mad!'

Such stories are not uncommon, particularly in those with long standing type 1 diabetes where both beta cell and counter regulatory function are absent. The variability of the insulin profile of subcutaneous isophane can be associated with wide swings in blood glucose despite meticulous attention to lifestyle and insulin administration technique. Such swings are particularly dangerous in those who have lost their awareness of hypoglycaemia and who may lapse into unconsciousness without warning. Such patients are driven to extraordinary measures to protect themselves and others. They may stop driving, stay constantly with a companion who can help them if necessary, test blood glucose many times during the day, and wake during the night to make sure they can safely go back to sleep. For many of these patients the consistency of the profile of basal analogues provides a welcome respite for both them and their partners.

As noted, the profile of the 'rapid' regular insulins is far from rapid with a peak of action well after the peak of glycaemia, while the insulin has ongoing effect even after blood glucose returns to baseline.

Case study 2

'After lunch my blood glucose goes so high I find it difficult to concentrate at work. I increased my quick insulin and the next thing I know I am low at 5.00 pm and have to have something to eat before I drive home. I have tried low GI foods but it still happens. If I increase my insulin I go low, if I don't I go high.'

One response, as occurred in this patient, is to try and vary the glycaemic index and glycaemic load of meals. Another is to shift the injection to 45 minutes before the meal but this may not be possible, acceptable or even effective. In such patients the bolus analogues may provide the answer and result in less early hyperglycaemia and/or later hypoglycaemia after meals.

In general, analogues are used more widely in type 1 than type 2 diabetes. As noted, they are associated with equivalent or modest improvements in glycaemic control with less hypoglycaemia, especially in type 1 diabetes. With the recent inclusion of glargine and detemir to the PBS, the use of basal analogues will increase. As in the USA where these newer insulins have been reimbursed for some time, the basal analogues are likely to become the insulins of choice for nonpregnant adults with type 1 diabetes. In general, it would seem reasonable to start patients with type 1 diabetes on both basal and bolus analogues. The new basal analogues should be substituted for traditional insulin in those patients with type 1 diabetes who are not meeting glycaemic targets, and particularly those with troublesome hypoglycaemia. The basal analogues may also be particularly appealing for patients with longstanding type 2 diabetes and cell failure with erratic control and hypoglycaemia unawareness, as well as those patients in whom the prospect of once daily basal insulin treatment may improve adherence. Some practical points to consider if switching from traditional to analogue insulins include:

- err on the safe side and decrease the insulin dose by 10–20%, particularly if changing from twice daily traditional basal to basal analogue treatment. Patients may need the same, a larger or a lesser dose of the analogue than the traditional insulin, but an episode of hypoglycaemia is not a good introduction to a new insulin
- increase the frequency of blood glucose testing and professional review. The profile of the analogues will be different from the traditional insulin and patients may experience hyper- or hypo-glycaemia at times different from those in the past.

Both these points are particularly important in those who are prone to hypoglycaemia, have had serious hypoglycaemic episodes requiring help from another person, or are hypoglycaemic unaware.

Future insulins and delivery devices

In Australia there are four insulin analogues available – two bolus and two basal. Elsewhere other analogues are in use and in the future more analogues may be developed. Future insulin analogues may have better profiles – the basal insulin truly 'peakless' and the bolus insulin more closely matched to prandial glycaemia. There may also be more reproducibility in their profiles and duration. Future developments may depend on the uptake of the current generation of analogues and the potential market for what might be real improvements rather than 'me too' versions.

The major improvement in insulin therapy for patients since the introduction of long acting insulin in the 1930s was the dramatic improvement in insulin delivery systems starting in the late 1970s with single use syringes followed by the insulin pen injectors in the 1980s. Insulin therapy today can be as simple as dial, inject and eat and the injections themselves are virtually painless.

Current insulin injection devices include the widely used insulin pens which are available for all insulin preparation and other devices for specific patient groups using a more limited range of insulins. For example, many older patients prefer the Innolet, a disposable device that is pre-loaded, looks like an egg timer, and has a large dial and convenient grip. Insulin injectors that automatically inject the insulin, or administer insulin using compressed air, make insulin therapy possible for patients who are unable to inject themselves or use needles. The most sophisticated subcutaneous insulin delivery devices are the insulin pumps, which are no longer bulky, awkward and uncomfortable to use.

Patients may appreciate these major improvements in injection devices but would like a life free from injections. A range of alternative routes for insulin delivery have been trailed including nasal and pulmonary.[13] Inhaled insulin has recently been approved for use in the USA. Unfortunately the devices are cumbersome, dosing inflexible and there is some concern regarding long term pulmonary toxicity. Furthermore, inhaled insulin is prandial insulin only, and there is still the requirement for injected basal insulin.

The ideal insulin delivery system would be an 'artificial pancreas', which seems within reach given the advances in implantation devices, automatic blood glucose monitoring and algorithms for insulin administration. Their arrival has long been expected, and the senior author remembers a meeting in the mid 1970s when it was announced that 'the technology is available to provide an artificial pancreas in the near future'. Nonetheless the current generation of these devices are producing promising results and perhaps the artificial pancreas will provide the long awaited cure for type 1 diabetes.

Summary of important points

- Available insulin therapy does not allow us to mimic endogenous insulin secretion.
- Bolus analogues have a more rapid onset and offset compared to traditional insulins, offer greater flexibility, have not consistently been demonstrated to decrease hypoglycaemia, but do achieve a small improvement in glycaemic control in patients with type 1 diabetes using basal-bolus insulin or continuous subcutaneous insulin infusions, ie. insulin pumps.
- Basal analogues offer a more peakless and reproducible profile compared to traditional basal insulins; are associated with a reduced rate of hypoglycaemia, particularly nocturnal hypoglycaemia; and offer at least equivalent glycaemic control to traditional basal insulins. Some studies show a small improvement in glycaemic control.

Conflict of interest: Dr PJ Phillips has provided advice, participated in company sponsored meetings and clinical trials, and received honoraria from all three companies marketing analogue insulins: Lilly, Novo Nordisk, Sanofi-Aventis.

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