Insulin analogues

What do they offer to the insulin KISS ('keep insulin safe and simple')?

The genetically engineered basal and bolus insulin analogues have profiles that more closely match pancreatic insulin secretion than the traditional basal and bolus insulins.

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The goal of insulin therapy is to achieve normoglycaemia or as near to it as possible without too much hassle or risk for the patient. Unfortunately the profiles of the traditional intermediate-acting and short-acting insulins and the traditional delivery systems (insulin vials and disposable syringes) are far from ideal, making the achievement of ideal glycaemic control difficult and causing episodes of hypoglycaemia. The newer genetically engineered insulin analogues and the newer insulin delivery systems involving disposable and reusable insulin injectors have considerable advantages over their precursors but are still not perfect. Currently there are five insulin analogues on the market: detemir (Levemir) and glargine (Lantus) are basal insulin analogues, and aspart (NovoRapid), glulisine (Apidra) and lispro (Humalog) are bolus insulin analogues.

This article outlines the limitations of the older insulin preparations and delivery systems and discusses the advantages and limitations of the insulin analogues. It also suggests ways to make best use of the available insulin analogues in type 2 diabetes, following the insulin KISS approach ('keep insulin safe and simple' – i.e. first control the fasting blood glucose level [BGL], then the evening BGL and then any mealtime BGL increases).[1-5]

Insulin therapy

The ideal

Ideally, therapeutic insulin would have a profile closely resembling the levels of insulin in a

IN SUMMARY

- **The first insulin analogue – the bolus insulin lispro – became available about 10 years ago.**
- **The basal insulin analogues detemir and glargine have relatively flat and reproducible profiles over 24 hours. Once-daily dosing with these insulins gives more constant and more predictable blood glucose levels than those associated with use of the isophane insulins.**
- **The bolus insulin analogues aspart, glulisine and lispro each have a quicker onset of action, a sharper peak and a shorter duration of action than neutral insulin. They may give better postprandial glycaemic control than neutral insulin, and less hypoglycaemia.**
- **Premix preparations of aspart and lispro are available. However, and at least when starting insulin, better glycaemic control, less weight gain and less hypoglycaemia is generally achieved using bedtime basal insulin and maintaining oral hypoglycaemics than using a premixed insulin.**
- **Insulin injectors are now used by most patients but patients should have syringes available and know how to draw up insulin from the insulin cartridge or prefilled injector in case their injector is broken.**

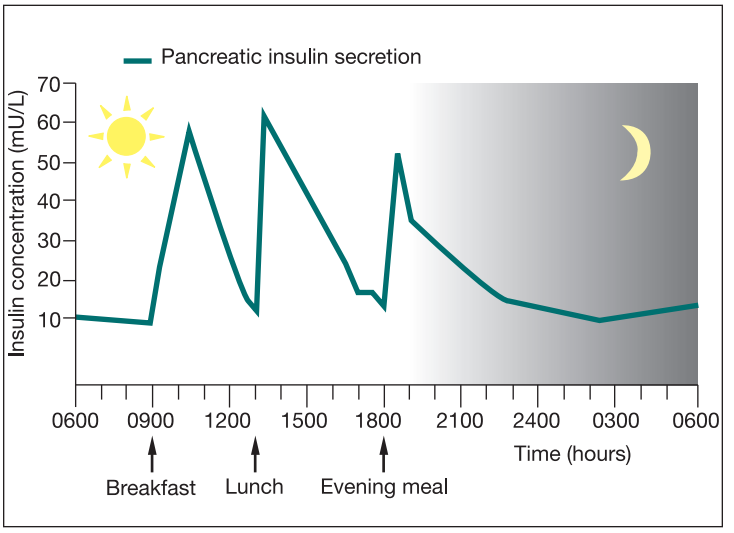

Figure 1. A normal 24-hour profile of insulin secretion.

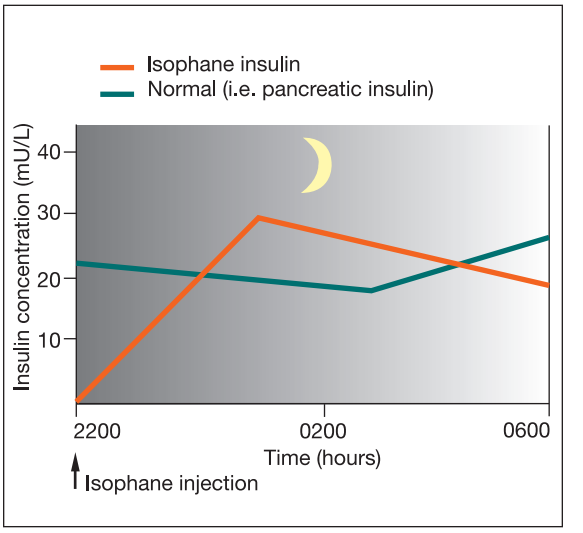

Figure 2. Night-time insulin profiles.

person without diabetes (Figure 1) and would be delivered into the portal circulation, as occurs with pancreatic insulin secretion.

In the ideal therapeutic insulin profile, a basal level of insulin would be maintained throughout the 24 hours. There would be a slight dip in insulin levels at night when many of the body's functions are at their 24-hour low (e.g. blood pressure, temperature and cortisol level all decrease), and a slight rise in the early hours of the morning as the body starts working (and blood pressure, temperature and cortisol level increase). When food is eaten, a bolus of insulin would match the nutrients being absorbed and minimise prandial excursions. Because the liver has a major role in controlling the flux and metabolism of absorbed nutrients, insulin would be delivered at a higher concentration in the portal circulation. Circulating insulin would be rapidly cleared so that insulin levels reflect the natural secretion of insulin in response to delivery of absorbed nutrients.

Available insulins and delivery systems

The currently available therapeutic insulins are the very quick-acting bolus and long-acting basal insulin analogues introduced over the past decade, the older quick-acting neutral insulin (also known as regular insulin and soluble insulin) and intermediate-acting isophane insulin, and biphasic mixtures of some basal and bolus insulins. Insulin preparations are discussed in more detail later in the article.

Most patients now use multidose insulin injectors to deliver insulin, as they are generally more convenient than insulin vials and disposable syringes. Pen injectors can be either disposable devices that are prefilled or reusable devices that can be reloaded using 3 mL cartridges. The disposable injectors are convenient but take up more storage room in the fridge and have a larger carbon footprint because of higher costs of manufacture, storage, transport and disposal. Older patients and those with limited vision or dexterity may prefer to use the larger prefilled disposable device known as InnoLet. This device is easily adjusted, has large numbers that are easy to see, is easy to grasp and has a plunger that is easily depressed. However, it is only available for use with certain insulins. (Details of the available insulins and their delivery devices are provided later in the article in Tables 1 and 3.) All patients using insulin injectors should also have syringes available and know how to draw up insulin from the insulin cartridge or injector in case their injector is broken.

Insulin pumps are an alternative to syringes and insulin injectors but at present are used by only a small proportion of insulin users, although the numbers are increasing. Insulin pumps have the capacity to continuously vary the rates of basal and bolus insulin delivery.

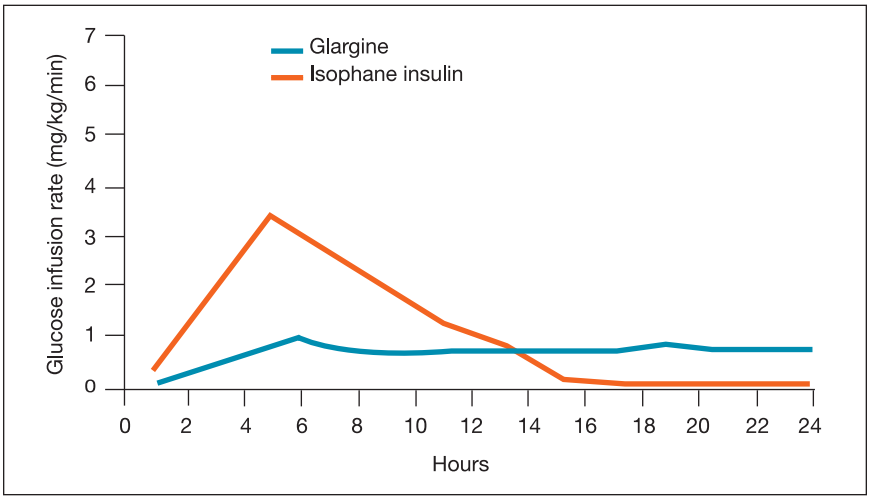

Figure 3. Time–action profiles of glargine and isophane insulin.

Limitations of therapeutic insulins and delivery systems

The current therapeutic insulin preparations and insulin delivery systems have several intrinsic limits, as discussed below.

Insulin delivery is not responsive

Insulin delivery is not responsive to circulating nutrient levels or to nutrient delivery. Although patients can measure the levels of one nutrient (glucose) and learn to assess the effects of current food intake of future nutrient/glucose levels, the measurement and assessment are often inaccurate and imprecise.

Insulin delivery is not on an 'as needed' basis

Insulin doses are deposited subcutaneously on several occasions in the day and are absorbed into the systemic circulation rather than being continuously and variably delivered into the blood of the portal circulation.

Although the rates of basal and bolus insulin delivery can be continuously varied using insulin pumps, dosage adjustments are under the control of the patient and are not reliably responsive to nutrient levels and delivery.

Some experimental systems continuously deliver insulin into the portal circulation but the same limitations apply as for subcutaneous continuous delivery. Also, the systems are difficult to install and maintain and have additional risks, including infection.

Insulin profiles are not ideal, or even close

The traditional intermediate and short-acting insulin preparations (isophane and neutral insulin, respectively) have profiles that are far from the basal and bolus insulin profiles of a person without diabetes. They have the added disadvantage of considerable variability.

The profile of isophane insulin is far from flat (Figure 2). If this insulin is given at night, levels often peak at the nadir of the body function and then fade as the body systems are awakening. This pattern is the opposite of normal physiology and may lead to hypoglycaemia during the night and hyperglycaemia in the morning. Variability of absorption results in variable effects on the basal insulin profile and unpredictable and variable BGLs.

Similarly the profile of neutral insulin is far from ideal. It lags behind the immediate postprandial rise in blood glucose and lingers despite the later fall in the glucose level. Variability of insulin absorption results in variable insulin levels and in variable and unpredictable postprandial BGLs.

Summarising the limitations

It is therefore no surprise that blood glucose control using traditional insulin delivery systems and insulin preparations is so difficult:

- insulin delivery is systemic rather than portal
- dosage adjustment is intermittent and not continuous
- assessment and anticipation of current and future nutrient levels and fluxes are imperfect
- insulin profiles are inappropriate and variable.

These limitations of insulins and delivery systems apply in both type 1 and type 2 diabetes but particularly in type 1 diabetes where the person is totally dependent on exogenous insulin to control nutrient metabolism (including glucose). The continuing endogenous insulin secretion in type 2 diabetes buffers mismatches between insulin requirements and exogenous insulin delivery and the limitations have much less effect.

The basal insulin analogues

Introducing the basal analogues

Theoretically, multiple injections over 24 hours of neutral insulin, which has a peak of action between two and five hours after injection and a duration of action of six to eight hours, could provide the necessary basal insulin between meals and overnight and bolus insulin at mealtimes. In fact, until the 1930s this is the way insulin was used.

Longer-acting preparations of insulin were developed in the 1930s by adding zinc or protamine (a basal protein extracted from fish sperm) to neutral insulin. The protamine and zinc insulins are insoluble and are absorbed more slowly than neutral insulin. Only the protamine-based longer-acting preparations are available in Australia now, the insulin zinc

Table 1. Basal insulins for use in type 1 and type 2 diabetes

Insulin preparation	Delivery devices			Comments
	Syringe (vials)	Prefilled multidose disposable device	Reusable device (loadable cartridges)	
Basal insulin analogues (long-acting)				
Detemir – Levemir	Not available	Available – FlexPen	Available – Penfill	PBS-subsidised for type 1 diabetes only
Glargine – Lantus	Available	Available – SoloStar	Available	Injection may sting Maximum dose 80 U in one injection Vials not PBS-subsidised for type 1 or type 2 diabetes
Traditional basal insulins (intermediate-acting)				
Isophane insulin (human)*				
– Humulin NPH	Available	Not available	Available – HumaPen	–
– Protaphane	Available	Available – NovoLet and InnoLet	Available – Penfill	InnoLet for patients with low vision and/or dexterity

* Bovine isophane insulin (Hypurin Isophane [NPH]) is rarely used nowadays. It is only available as vials for use in syringes.

suspensions having been withdrawn in 2005. In the manufacture of the protamine preparation (which is known as isophane and also as neutral protamine Hagedorn [NPH] after its developer), neutral insulin binds to the protamine and is precipitated as crystals, resulting in a cloudy solution. Once all the interaction sites are associated with insulin ('neutralised'), the absorption profile of further neutral insulin added to isophane is unaffected. Isophane is the basis for all the intermediate-acting and premixed insulins available in Australia.

Using isophane as basal insulin has made life much easier for people living with type 1 diabetes. However, its peaked profile and variability of absorption causes the previously discussed problems associated with a relatively short duration of action and a variable activity profile.

In the past decade, pharmaceutical companies have successfully genetically engineered the insulin molecule and developed the insulin analogues. Of the two currently available long-acting insulin analogues, glargine was marketed first, in the early 2000s, followed by detemir a few years later. Compared with isophane, they have relatively flat and reproducible profiles over 24 hours (Figure 3). They therefore avoid many of the problems associated with isophane. Although both are TGA-approved for use in type 1 and type 2 diabetes, currently glargine is PBS-subsidised for use in both type 1 and type 2, whereas detemir is PBS-subsidised for use in type 1 diabetes only. Both are more expensive than isophane. The available analogue and traditional basal insulins are listed in Table 1.

Glargine and detemir in detail

Glargine has an amino acid substitution in its molecule that makes it soluble at an acid pH and insoluble at the pH of body fluids. Glargine therefore precipitates at the site of injection, and the precipitated crystals then slowly dissolve, releasing the insulin for absorption.

The amino acid sequence of the detemir molecule has been altered by omitting an amino acid and replacing it with a short chain fatty acid. This makes the insulin soluble and also causes it to associate with albumin in the interstitial fluid and bloodstream. This association with albumin slows both the absorption of insulin from the injection site and its transfer from the bloodstream to the interstitial fluid of tissues and then to the insulin receptors of the target cells.

As both basal analogues are soluble in their delivery formulations, the contents of the vials or other delivery devices do not require mixing before use to ensure that reproducible amounts of basal insulin are injected – as is necessary with isophane insulin. Neither basal analogue can be mixed with bolus insulins.

In patients with type 1 diabetes, clinical trials of both basal analogues compared with traditional basal insulins have shown improvement in A_{1c} levels and fewer nocturnal hypoglycaemic episodes.[6,7] In patients with type 2 diabetes, in whom there is still some endogenous insulin secretion to blunt blood glucose swings, these advantages are less clear. In both patients with type 1 diabetes and those

Table 2. Basal insulin analogues – pros and cons

Pros compared with isophane insulin	Cons compared with isophane insulin
• Consistent profile	• Slower response to dose changes than with isophane insulin
• Often single daily dose	• May be confused with bolus insulins as both are clear solutions
• Less hypoglycaemia than with isophane insulin	• Cannot be mixed with bolus insulins*
• No mixing or resuspension needed for injection	• Glargine may sting when injected

* Little data on safety or efficacy available.

with type 2 diabetes, the basal insulin analogues are absorbed over a longer period than isophane and usually only single daily injections of the analogues are needed. The pros and cons of analogue basal insulin compared with traditional basal insulin are summarised in Table 2.

Some trials have suggested that the use of detemir is associated with less weight gain compared with other insulin preparations, and even with some weight loss.[6]

Using basal insulin analogues in type 2 diabetes

The KISS approach to starting insulin in type 2 diabetes first targets the patient's fasting BGL – that is, before breakfast – and then, if necessary, the BGL before the evening meal.[1-5] In some patients, the BGL before the evening meal is targeted first, and then the fasting BGL. The basal insulins target these 'basal' blood glucose values.

The same 'rules' apply when initiating insulin therapy whether analogue or isophane is used as the basal insulin. Start with 10 units of basal insulin, usually at bedtime (to fix a high fasting BGL), and titrate the dose twice weekly to achieve the target fasting BGL (see the box on basal insulin titration on this page).[1,8] In the occasional patient in whom the fasting BGL is on target but the evening preprandial BGL is high, the basal insulin should be given before breakfast.

Basal insulin titration[1]*

Start with 10 units of basal insulin.
Adjust the dose twice weekly, to reach the target fasting BGL of <6 mmol/L, using the guidelines below:

Mean fasting BGL over preceding 2 days (mmol/L)	Insulin increase (U/day)
>10	8
8 to 10.0	6
7 to 7.9	4
6 to 6.9	2

- Do not increase the insulin dose if the fasting BGL is <4 mmol/L at any time in the preceding week.
- The insulin dose may be decreased (small decreases of 2 to 4 units) if there is severe hypoglycaemia (requiring assistance) or the BGL is <3.0 mmol/L in the preceding week.

* Adapted from *Diabetes Care* 2003; 26: 3080-3086.[8]

Delivery systems

Often the particular basal insulin preparation is chosen not because of its absorption profile but because of the desired method of injection and the availability of that method for that particular insulin preparation. The delivery devices available for the analogue and traditional basal insulins are listed in Table 1.

Potential problem – insulin not lasting long enough

Sometimes the basal insulin analogues 'run out' and do not control the blood glucose towards the end of their duration of action.

For example, a bedtime injection of basal insulin analogue may control the fasting BGL but still be associated with a high BGL before the evening meal. In this case, increasing the insulin dose at bedtime would cause morning hypoglycaemia. The problem of morning hypoglycaemia could be solved by shifting the basal insulin injection to the morning but then the basal insulin from the morning injection may 'run out' overnight and result in morning hyperglycaemia. The better solution would be to use two doses of basal insulin analogue – the morning dose to control basal blood glucose before the evening meal and the bedtime dose to control overnight and fasting glycaemia.

Potential problem – insulin lasting too long

On other occasions the opposite occurs.

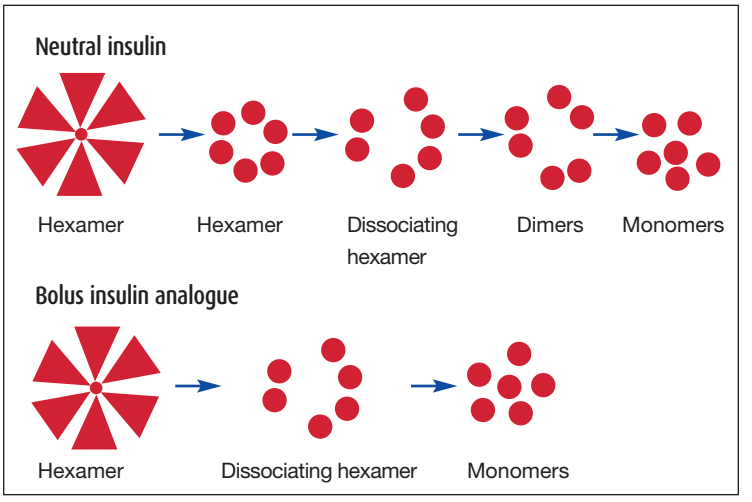

Figure 4. Dissociation of bolus insulins.[9]

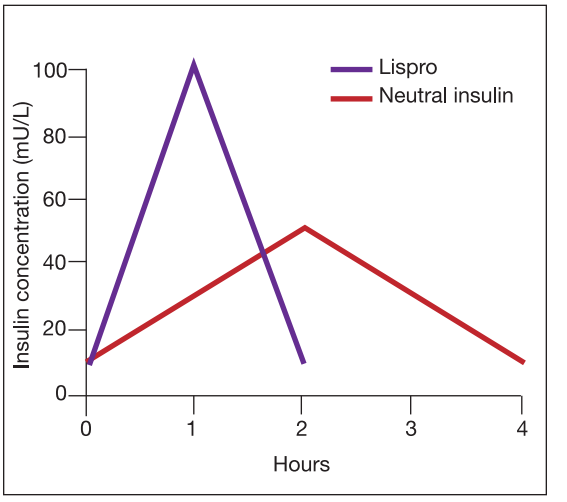

Figure 5. Time–action profiles of lispro and neutral insulin.

The basal insulin analogue controls the basal blood glucose 12 hours after injection but causes hypoglycaemia towards the end of its duration.

For example, a bedtime injection of basal insulin analogue may not be controlling the fasting BGL but be associated with hypoglycaemia before the evening meal. Shifting the insulin dose to the morning would probably make things worse because the insulin injected in the morning would be likely to be less available overnight, therefore increasing the fasting blood glucose, and more available during the day, therefore worsening hypoglycaemia before the evening meal.

In this situation, the prolonged duration and relatively flat profile of the basal insulin analogues are the problem – these insulins last too long and have too flat a profile. More insulin activity is required during the first 12 hours (in this case during the night) and less in the second 12 hours (in this case during the day). The shorter duration and peaked profile of isophane are advantageous in this situation, and either the addition of a bedtime dose of isophane or a switch to twice-daily isophane would control the fasting blood glucose but not result in hypoglycaemia before the evening meal.

The bolus insulin analogues

Introducing the bolus analogues

The insulin monomers of neutral insulin injected into subcutaneous tissues aggregates into dimers and hexamers, which then gradually dissociate to monomers that are absorbed.[9] Bolus insulin analogues have been genetically engineered to reduce the affinity between insulin monomers and they therefore dissociate and are absorbed more quickly than neutral insulin (Figure 4).

Three analogue bolus insulins are available in Australia: lispro was the first, in the late 1990s, followed by aspart in 2005 and then glulisine in 2007. All three insulins are subsidised by the PBS for use in both type 1 and type 2 diabetes, and they cost only marginally more than neutral insulin. The available analogue and traditional bolus insulins are listed in Table 3.

The profiles of lispro, aspart and glulisine are similar. Compared with neutral insulin, they reach twice the peak in half the time and have half the duration of action (Figure 5).[10]

In clinical trials, the theoretical advantages of bolus analogues over traditional bolus insulin in terms of glycaemic control and hypoglycaemia are less apparent than the advantages of basal analogues in patients with type 1 diabetes.[11,12] There are fewer trials comparing analogue with traditional bolus insulin in type 2 diabetes and less evidence of superiority.

Bolus insulin analogues may have advantages in patients with type 1 diabetes but there are also potential disadvantages (Table 4). The same pros and cons apply to use in patients with type 2 diabetes but, as for the basal analogues, they apply to a lesser degree because the endogenous insulin secretion in patients with type 2 diabetes decreases blood glucose swings compared with those in patients with type 1 diabetes.

Using the bolus insulin analogues in type 2 diabetes

In the KISS approach to starting insulin in type 2 diabetes, usually a single injection of basal insulin and continuation of oral hypoglycaemic agents controls not only the fasting BGL but also BGLs over the 24-hour period.[1-5] As noted earlier, occasionally a second injection of basal insulin is required to control the evening prepran - dial BGL.

Once the fasting BGL has been fixed and the evening preprandial BGL tackled, the next step is to consider stopping or reducing all or some of the oral hypoglycaemic agents. Generally metformin is continued because of its advantages in

Table 3. Bolus insulins for use in type 1 and type 2 diabetes

Insulin preparation	Delivery devices			Comments
	Syringe (vials)	Prefilled multidose disposable device	Reusable device (loadable cartridges)	
Bolus insulin analogues (very quick-acting)				
Aspart – NovoRapid	Available	Available – FlexPen	Available – Penfill	–
Glulisine – Apidra	Not available	Available – SoloStar	Not available	Maximum dose 80 U in one injection Vials not PBS-subsidised
Lispro – Humalog	Available	Not available	Available – HumaPen	–
Traditional bolus insulins (quick-acting)				
Neutral insulin (human) – Actrapid – Humulin R	 Available Available	 Not available Not available	 Available – Penfill Available – HumaPen	 – –

* Bovine neutral insulin (Hypurin Neutral) is rarely used nowadays. It is only available as vials for use in syringes.

reducing insulin resistance and helping reduce weight gain, although the daily dose and frequency of dosing may be reduced. As both insulin and glitazone therapy are associated with sodium retention, therapy with pioglitazone (Actos) should be reconsidered (as from October 2008, rosiglitazone has not been subsidised by the PBS for use with insulin). The sulfonylureas may still increase beta cell insulin secretion but could be stopped and then restarted should hyperglycaemia occur that could not be controlled by adjusting the basal insulin. The incretin (specifically glucagon-like peptide-1 or GLP-1) enhancer sitagliptin (Januvia) and mimetic exenatide (Byetta) are not approved for combined use with insulin.

The next step is to consider whether hyperglycaemia is occurring between breakfast and the evening meal or after the evening meal. Finding and fixing these 'hypers' involves reviewing the patient's BGL records and considering lifestyle intervention – reducing mealtime glycaemic load at breakfast or the evening meal or increasing activity after those meals. If lifestyle interventions are not feasible or have not controlled the 'hypers', the options are adding and titrating acarbose (Glucobay) at breakfast and/or the evening meal or adding a bolus insulin before those meals. The theoretical advantage of adding acarbose is a lack of weight gain or hypoglycaemia, both of which may occur with mealtime bolus insulin. The practical disadvantage is the need to start acarbose at a low dose and titrate the dose slowly, and the potential for gastrointestinal side effects (particularly bloating and flatulence). Starting acarbose at 25 mg before the meal and titrating as needed at one to two-week intervals to a maximum dose of 200 mg minimises the gastrointestinal side effects and may control postprandial glycaemia after breakfast and before lunch and/or after the evening meal.

If postprandial glycaemia is still a problem, as indicated by A_{1c} levels still being high, the final step is to start bolus insulin therapy and titrate the dose to control prandial glycaemia. The recommended safe and simple guide is:[1]

- start with 10% of the total daily basal dose
- increase or decrease the dose by 20% when the postprandial BGLs are well off target and by 10% when values are closer.

Blood glucose monitoring equipment and techniques should also be checked, and patients should be reminded to record all their test results, not just the 'good' values.

Delivery systems

As for basal insulin, choosing the bolus insulin depends on the required insulin profile (very quick-acting or quick-acting) and the preferred injecting device (syringe, disposable injector or reusable injector).

Usually patients prefer to use the same device type for their bolus insulin as they are already using for their basal insulin. As long as the devices for the two insulin types can be easily differentiated, this is sensible. However, using the same injecting device type increases the chance of the patient giving a wrong dose of insulin – a bolus dose of a basal insulin

Table 4. Bolus insulin analogues – pros and cons

Pros compared with neutral insulin	Cons compared with neutral insulin
• Inject when eating • Less hypoglycaemia than with neutral insulin • Better postprandial glycaemic control than with neutral insulin	• Need to eat promptly after injection • Possible insulin 'run out' before next meal • Need adequate carbohydrate in meal

or vice versa. This mistake is especially likely if analogue basal insulin is used because then the basal and bolus insulins are both clear solutions – and not differentiated by the cloudiness of the isophane basal insulin.

Sometimes the device type used for the basal insulin is not available for the bolus insulin. In this case the choice is between having two different injectors or changing to a different basal and/or bolus insulin so the same injector type can be used for both. The delivery devices available for the analogue and traditional bolus insulins are listed in Table 3. Unfortunately the InnoLet injecting device is not available for a bolus insulin.

Potential problem – insulin too quick and too peaked

The rapid onset and high peak concentration of the analogue bolus insulins may cause hypoglycaemia if inadequate amounts of carbohydrate are eaten, such as after the classic Australian meal of steak and salad. Ensuring meals have a carbohydrate component – bread, potato, pasta or rice – should avoid such hypoglycaemia.

Potential problem – insulin not lasting long enough

The rapid offset of the analogue bolus insulins may mean that the insulin level before the next meal is inadequate to control basal glycaemia – that is, the insulin 'runs out'. Simply increasing the bolus dose in an attempt to counteract this may cause postprandial hypoglycaemia.

The options in this situation are to have the first meal later or the second meal earlier so the analogue bolus insulin is still working before the second meal, to increase the basal insulin dose or to switch from the analogue bolus insulin to a traditional bolus insulin, which will have a longer duration of action. Probably the simplest and best solution in this case is to use a traditional bolus insulin. Insulin therapy should, in principle, fit the patient's lifestyle, not vice versa, and shifting a meal may affect people other than the patient. Increasing the dose of basal insulin, which has been controlling basal daytime and night-time glycaemia, is likely to cause hypoglycaemia.

A word about premixes

Some practitioners hope that 'one size will fit all' and use premixed insulin preparations that contain basal and bolus insulins in fixed proportions. For clothing, one size – extra large – does fit all, although not very comfortably or elegantly. For insulins, however, one size – premixed – often doesn't fit and also causes problems. The quick-acting insulin can cause hypoglycaemia and extra weight gain, and the fixed proportions of short-acting insulin and longer-acting insulin can make titration difficult because changing the dose changes both bolus and basal components at the same time.[13] Generally, and at least when initiating insulin therapy, using a bedtime basal insulin dose and maintaining oral hypoglycaemic agents produces better glycaemic control, less weight gain and less hypoglycaemia than twice daily basal insulin, twice daily premixed insulin or basal/bolus insulin schedules.[13]

The bolus insulin analogues cannot be mixed with the basal insulin analogues. However, aspart and lispro can be mixed with their respective protamine-based longer-acting preparations (aspart

protamine suspension and lispro protamine suspension) to form biphasic mixtures (Humalog Mix25, Humalog Mix50, NovoMix 30). These mixes have profiles similar to those of the traditional premixed biphasic insulins (i.e. mixed neutral and isophane insulins) apart from the initial faster onset of action. A premix is not available for glulisine.

Conclusion

The genetically engineered insulin analogues and the insulin delivery systems involving disposable and reusable insulin injectors have considerable advantages over their traditional precursors but are still not perfect. The basal and bolus insulin analogues were developed to match basal pancreatic insulin secretion and pancreatic insulin secretion in response to glycaemia better than the previously available basal and bolus insulins.

The basal analogues detemir and glargine have relatively flat and reproducible profiles over 24 hours compared with the older basal insulin, isophane. Once-daily dosing with these insulins gives more constant and more predictable BGLs than those associated with the use of isophane. Sometimes and in some patients, however, they may not last long enough ('run out') and may not control the blood glucose towards the end of their duration of action. At other times, they may last too long and have too flat a profile if different insulin activities are required at different times of the day.

The bolus analogues aspart, glulisine and lispro have quicker onset of action, a sharper peak and a shorter duration of action than the older bolus insulin, neutral insulin. They may give better postprandial glycaemic control than neutral insulin, and less hypoglycaemia. However, their rapid onset and offset and high peak concentrations may cause problems of postprandial hypoglycaemia and/or pre-prandial hyperglycaemia later, relating to their acting too quickly or not lasting long enough, respectively. MT

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