Insulins in 2002

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SYNOPSIS

The new soluble long-acting insulin analogues have a longer and more consistent action than the traditional crystalline preparations. The new short-acting analogues provide a quick onset, sharp peak and quicker offset than neutral insulin. They can be given immediately before eating. Compared to human insulin, they may control postprandial hyperglycaemia better and result in less hypoglycaemia between meals. The hypoglycaemic potency of short-acting analogues is similar to neutral insulin but when changing from one to the other, insulin doses should be reduced to minimise the risk of hypoglycaemia.

Index words: metformin, diabetes.

Introduction

Our knowledge and use of insulin has been continuously evolving since its discovery in 1921 (Table 1). The short delay between the discovery of insulin and its commercial production and distribution was amazing (nothing like the decade or so it would take now). In the 1930s there was the drive to produce long-acting preparations. After that not much happened until the 1970s when insulin preparations were purified and U100 (100 U/mL) became standard.

In the 1980s, human insulin was produced by recombinant DNA technology. This technology was then used to synthesise insulin analogues. Insulin delivery devices improved and patients began to have choices other than syringes (e.g. pen injectors, insulin pumps).

Over the last 10 years the pharmaceutical industry has prepared various insulin analogues (short- and long-acting) and tested new ways and new routes for insulin delivery. In 2002 we have insulin preparations that have the potential to reduce the frequency and amplitude of blood glucose swings and hypoglycaemia. This will allow patients to achieve better overall glycaemic control.

*Table 1*

Insulin – the continuing evolution

1921	Discovery
1920s	Production
1930s	Long-acting protamine/insulin zinc suspension
1970s	Mono component insulin
	Unit 100
1980s	Human insulin
	Insulin pens
1990s	Insulin analogues
2000s	Insulin smorgasbord

Can insulin treatment mimic nature?

An ideal regimen for insulin would reproduce normal pancreatic secretion (Fig. 1). There would be a basal output of 0.5–1 unit per hour (reducing during the night and increasing in the early morning) with mealtime surges (boluses) of 5–10 units to cover the ingestion of nutrients. The insulin would be delivered into the portal circulation and thus have extra effects on liver metabolism. Insulin delivery would be instantly responsive to the ambient blood glucose. The traditional crystalline* preparations and neutral human insulin cannot mimic nature.

Fig. 1

A normal 24 hour profile of insulin secretion[1]
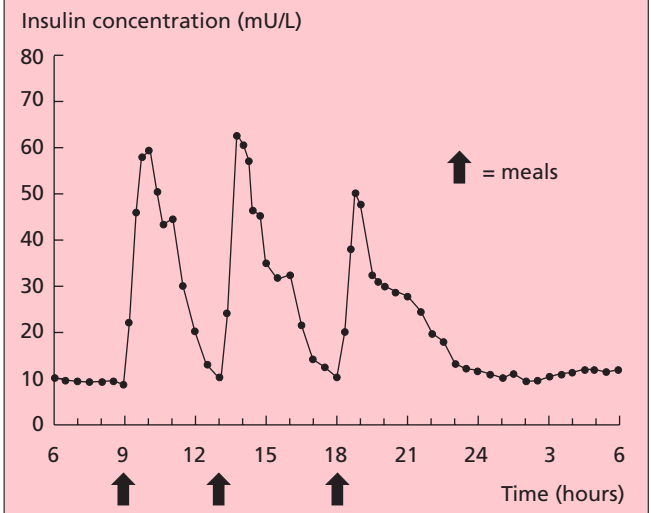
Insulins before the analogues – intrinsically inadequate

Available preparations were delivered systemically and with variable absorption both between (e.g. abdomen versus leg) and within sites. Even the longest-acting human insulin (ultralente) often did not cover the full 24 hours and insulin injected in the evening peaked during the night and was 'running out' in the morning. The action of short-acting neutral insulin did not match nutrient input. It was slow to start (e.g. 45 minutes), did not peak until two hours after injection and was still there after 5–6 hours. Even when patients did inject 30–40 minutes before eating (as recommended but rarely practised) the concentration profile was still too blunt. Despite these apparent pharmacokinetic shortcomings the older insulins were and still are satisfactory for some patients.

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* Insulin crystals are formed when protamine and/or zinc are added (neutral protamine Hagedorn (NPH), or insulin zinc suspension (IZS)). The crystals slowly dissolve and release insulin over a prolonged period.

Insulin after the analogues – better but still not ideal

The profiles of the new basal and bolus analogues allow patients to match pancreatic insulin secretion more closely than they could with the older insulins. However, the lack of portal delivery, night-time dip, morning surge and response to ambient blood glucose are still problems.

'Basal' insulins

The absorption profile of new basal insulin preparations is longer, flatter and more reproducible than previous long-acting preparations (IZS, NPH). Two types of basal insulin analogues are being studied in Australian clinical trials but they are not yet generally available.

Insoluble insulins (e.g. insulin glargine)

Changing the amino acid composition of insulin changes its solubility in subcutaneous tissues. The insulin analogue is soluble in acidic solution (in the vial) but insoluble at body pH. After injection crystals form and the insulin is then absorbed slowly.

Insulin fatty acid complex (e.g. Detemir)

When a fatty acid is attached to the insulin molecule the complex binds to albumin in the subcutaneous space and in the plasma. The insulin gradually dissociates from albumin and is then able to diffuse from the subcutaneous space into the blood stream to later gain access to the tissue insulin receptors.

'Bolus' insulins

Before moving from the subcutaneous tissues to the blood stream insulin monomers must dissociate from the hexamers present in neutral insulin preparations. This dissociation slows and prolongs the absorption profile. The amino acid compositions of the 'bolus' analogues make it easier for insulin molecules to dissociate in the subcutaneous tissue. Absorption is quicker and less prolonged. Lispro insulin achieves these effects because the positions of lysine and proline in the B chain (Lys B28 Pro B29) are switched. In insulin aspart, aspartic acid is added to the B chain (Asp B28). Both these analogues are available on the Pharmaceutical Benefits Scheme.

Insulin delivery – now patients have a choice

In 1921 patients injected large volumes of impure insulin with reusable glass syringes and large gauge needles (that they re-sharpened periodically). Often there was inflammation at injection sites and insulin antibodies modified the pharmacokinetic profile. In 2002 patients use subsidised pen injectors or disposable syringes with fine needles which make injection less painful. Patients can also use an insulin pump that delivers insulin subcutaneously at rates that can be varied to closely match the normal profile of insulin secretion (including night-time dip, morning surge and mealtime boluses).

In clinical research programs, insulin pumps have been implanted to deliver insulin into the peritoneal cavity (and thus into the portal circulation). Infusion rates are controlled by radio and insulin reservoirs are filled intermittently through a special port.

Clinical trials of oral, nasal and inhaled insulin are continuing and several pharmaceutical companies have developed new formulations and delivery devices.

Starting insulin in type 2 diabetes – sooner rather than later

The United Kingdom Prospective Diabetes Study[2] showed that type 2 diabetes is a progressive disease and that patients require increasing doses and numbers of oral hypoglycaemic drugs. Many patients eventually require insulin. However, patients and doctors are often reluctant to start it and between them they can put off the decision for years. The recommended target HbA1c is less than 7% with an 'action limit' of 8% but many patients have higher values for long periods of time. In general the higher the concentrations of blood glucose and HbA1c the greater the benefit of reducing them and the less the 'cost' of inconvenience, stress and hypoglycaemia.[3] Once the decision to start insulin is made, both patient and doctor are almost invariably surprised how easy it is and both feel much better (the patient physically and the doctor professionally).[4] Moreover patients appreciate reducing the numbers and costs of their tablets.

Insulin schedules – one size does not fit all

Weight gain and hypoglycaemia are problems when starting treatment irrespective of whether a new or old formulation of insulin is used. Recent trials have compared different regimens for starting insulin in patients with type 2 diabetes.[5] Bedtime intermediate insulin and twice-daily metformin (and stopping other oral hypoglycaemic drugs) was associated with the best glycaemic control and least weight gain and hypoglycaemia. In patients already taking metformin, an evening dose of NPH insulin, to control night-time and fasting blood glucose, with daytime doses of metformin might be a suitable starting schedule. This schedule reduces insulin resistance and weight gain in those patients, often obese, who are particularly insulin resistant and prone to weight gain with insulin therapy.

A similar trial has not been done with the other class of drugs which increases insulin sensitivity (thiazolidinediones, e.g. rosiglitazone) but they may be suitable in some patients starting insulin. However, the 'glitazones' may be associated with increased fluid accumulation which can cause problems in patients with cardiac failure.

Combining insulin secretagogues (sulfonylureas – long-acting, glitinides – short-acting) with insulin is less appealing theoretically since one could use more long- or short-acting insulin as needed rather than add a further medication. However, they may have advantages in selected patients (for example, a glitinide may be helpful if postprandial hyperglycaemia is a problem). Similarly acarbose could theoretically be used with insulin for patients where postprandial hyperglycaemia was a problem.

As a rough guide, patients require a total daily insulin dose of half to one unit for each kilogram of their ideal weight.[†]

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† As an approximation,

ideal healthy weight (kg) = height (cm) – 100

For example, in a 178 cm man the healthy weight is 78 kg. His total daily dose at 0.5 units/kg would be 39 units (26 units in the morning and 13 units in the evening).

Generally daytime requirements are two-thirds and night-time requirements one-third of the total. If daytime oral hypoglycaemic agents (e.g. metformin) are used, the night-time dose might be used without the morning dose. If short-acting insulin is required, the 'two-thirds, one-third' rule is useful as a starting point (two-thirds long-, one-third short-acting insulin).[6]

The bolus analogues give an insulin profile which is closer to the normal secretion pattern. They have better control of postprandial hyperglycaemia and less risk of hypoglycaemia between meals than injections of regular human insulin. Moreover, the new analogues can be given immediately before a meal rather than 30–45 minutes beforehand as recommended for neutral human insulin.

Occasionally the quick 'on and off' of the analogues proves a disadvantage. Patients must eat after the injection since the insulin peaks rapidly and occasionally they 'run out' before the next dose and their blood glucose increases. Some patients prefer the slower onset and offset of the older bolus preparations. Similarly, in some patients the shorter, more peaked profile of the older basal preparations might be preferred (for example where a morning injection of a new basal analogue results in hyperglycaemia during the middle of the day).

In theory, the overall potency of the quick-acting analogues is similar to regular neutral insulin, but in practice, effects in individual patients will vary. As usual when changing insulin it is wise to use smaller doses to start with to reduce the risk of unexpected hypoglycaemia.

The analogues can be mixed with long-acting insulins of the same brand if the insulins are injected immediately after mixing. One pre-mix is available (75% of long-acting insulin[‡] and 25% of lispro).

Pre-mixes – panacea or problem?

The most commonly used insulin preparation in Australia is a pre-mixed insulin (NPH and neutral) using a pen injector. This is convenient for the patient – 'dial and shoot'– and the doctor does not have to make a choice between the 10 long-acting and 10 short-acting insulin preparations.

However, there can be problems with fixed combinations. They have limited flexibility as changing the dose changes both long- and short-acting components. Patients often use a fixed dose which may suit their requirements on one day, but cause blood glucose swings on another when their activity or eating schedule changes. Moreover the daytime NPH puts them at risk of hypoglycaemia and requires them to eat in the middle of the day. Patients may find it easier to achieve targets for glycaemic control when they can adjust their insulin regimen to their lifestyle, rather than fitting their lifestyle to their insulin.

[‡] NPL, insulin lispro protamine suspension (equivalent to NPH where human neutral insulin has been replaced by lispro).

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FURTHER READING

See resources on the following web site:
www.diabetes.org.au/

Self-test questions

The following statements are either true or false (answers on page 47)

1. The amino acid structure of insulin glargine enables the insulin to be rapidly released into the circulation.
2. Patients taking insulin should usually inject two-thirds of their total dose during the day and one-third at night.

Australian Prescriber wallchart

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