Insulin lispro for the treatment of type 2 diabetes

Miles Fisher

Tight control can prevent complications in type 2 diabetes, and many patients will require insulin therapy to achieve this. Newer insulin formulations may offer some advantages with regard to patient convenience and a reduction in hypoglycaemia.

Type 2 diabetes (previously non-insulin-dependent diabetes, NIDDM) is a heterogeneous metabolic syndrome comprising variable degrees of insulin deficiency (defective insulin secretion = beta cell dysfunction) and impaired insulin action (= insulin resistance) (DeFronzo, 1992). Some patients may be controlled by diet alone in the early stages of the disease, but many patients require oral antidiabetic drugs because of the degree of beta cell dysfunction at the time of diagnosis. Later, as the underlying beta cell dysfunction worsens, oral hypoglycaemic agents become ineffective and each year around 10% of patients with type 2 diabetes are converted to therapy with insulin (*Table 1*).

The conversion to insulin is not without problems. Patients may initially be fearful of self-injection, although this is less common when modern pen injection devices and fine needles are used. Patients require careful education about all aspects of insulin administration, including the timing of injections in relation to meals, which is usually taught by diabetes nurse specialists. Type 2 diabetes is much more prevalent than type 1 diabetes, and the conversion to insulin therapy is a commoner clinical picture than a newly presenting patient with type 1 diabetes, so this activity has major resource implications in diabetic clinics.

TABLE 1.
Indications for insulin in patients with type 2 diabetes

Poor glycaemic control on maximum oral agents
Severe symptoms (tiredness, weight loss)
Intercurrent illness (e.g. surgery, myocardial infarction)
Amyotrophy or painful neuropathy
Pregnancy

Once these initial hurdles are passed, the principal side-effects of insulin therapy are weight gain and hypoglycaemia (Amiel, 1999). Patients who are converted from oral agents to twice daily fixed mixtures of insulin gain up to 4 kg in weight (Yki-Jarvinen et al, 1992). Clinical staff who look after people with diabetes are often surprised that they are unwilling to accept the risk of hypoglycaemia, and are prepared to risk the development of diabetic complications. This is rarely a surprise to people with diabetes, who live under the shadow of hypoglycaemia on a daily basis (Frier, 1999). The fear of hypoglycaemia is the most common reason why patients are unable to achieve the targets of glycated haemoglobin desired by their medical carers (Pramming et al, 1991).

UK PROSPECTIVE DIABETES STUDY

The United Kingdom Prospective Diabetes Study (UKPDS) proved beyond doubt that the control of blood glucose reduces the microvascular complications of type 2 diabetes (UKPDS Group, 1998a,b). Following a complex treatment protocol, patients aged 25–65 years with newly diagnosed type 2 diabetes were allocated to either conventional or intensive therapy and followed for a median of 10 years. In addition to fewer microvascular complications, patients allocated to the intensive treatment group had a lower risk of any diabetes-related endpoint than patients in the conventional treatment group, and there were insignificant reductions in diabetes-related deaths and all-cause mortality.

Dr Miles Fisher is Consultant Physician in the Royal Alexandra Hospital, Paisley PA2 9PN

The target fasting blood glucose in the intensive group was 6 mmol/litre, and the mean glycated haemoglobin (HbA1c) attained in this group was 7.0%. To reach and maintain this degree of glycaemic control required frequent adjustments to treatment.

Within the intensive treatment group, patients were initially receiving either sulphonylureas or insulin, but many patients who were initially allocated to the sulphonylurea group required conversion to insulin therapy at an early stage to try and maintain the HbA1c within the target range.

HYPOGLYCAEMIA IN THE UKPDS

The degree of protection against microvascular complications was independent of whether treatment was with tablets or insulin, and there was no threshold or cut off for reductions in complications. Patients in the intensive group had many more hypoglycaemic episodes than patients in the conventional group. The rates of major hypoglycaemic episodes (requiring help from a third party or medical intervention) per year were 0.7% with conventional treatment, 1.0% with chlorpropamide, 1.4% with glibenclamide and 1.8% with insulin.

The insulin regimens that were used in the UKPDS reflected both prescribing practice when the study was conceived and the habits of the principal investigators in Oxford. Initial therapy was with a once-daily injection of intermediate or long-acting insulin (isophane or ultratard) as a background insulin, with the addition of short-acting (soluble) insulin if targets were not met or the total daily dose of insulin was greater than 14 units. This insulin regimen, now called 'basal-bolus insulin', is commonly used in the UK to treat patients with type 1 diabetes, and is only occasionally used by people with type 2 diabetes because of the frequency of the injections and accompanying blood glucose monitoring.

INSULIN PHARMACOKINETICS

Insulin is a large peptide that is not chemically stable. When stored in vials conventional soluble/regular insulin tends to aggregate into hexamers, where six insulin molecules aggregate together to maintain chemical stability. When injected subcutaneously it slowly dissociates into dimers and then monomers before it can be absorbed into the circulation.

This process takes time, and patients are advised to leave at least 20 minutes between injections and meals, so that the onset of the metabolic action of the injection coincides with the absorbtion of carbohydrate from the gut. This delay is a nuisance, and many patients ignore the advice of health-care professionals and inject their insulin immediately before a meal. This delays the peak of insulin action relative to the meal, and when combined with the duration of action of soluble insulin can lead to hypoglycaemia before the next main meal. To combat this problem patients are advised to take mid-morning snacks to try and avoid mid-morning hypoglycaemia, but at a cost of further weight gain.

A second problem concerns the time–action profile of the intermediate-acting insulin component of the fixed mixture. All of the currently available intermediate- and long-acting insulins have a peak action that occurs between 4 and 12 hours after injection, and the duration of action may last between 16 and 32 hours. The onset of the morning intermediate injection can be timed to coincide with the lunchtime meal, but the onset of the second intermediate injection often occurs several hours after the last ingestion of food, when the soluble insulin is still having an effect and when the patient is sleeping. This is a major cause of nocturnal hypoglycaemia.

INSULIN ANALOGUES

Insulin analogues are produced using recombinant DNA technology, with alterations to the DNA sequences to produce peptides with differing amino acids from native human insulin (Barnett and Owens, 1997). Insulin-like growth factor 1 is the mediator of the action of growth hormone in the body. It shares many amino acid sequences with insulin, but does not have a tendency to aggregate into hexamers.

It was possible to identify the amino acids which were responsible for the lack of aggregation, and to mimic this in the insulin molecule by reversing the amino acids proline and lysine at the 28 and 29 positions in the B-chain of insulin (Koivisto, 1998) (*Figure 1*). The result was lispro, an insulin analogue with less tendency for self-association, which has a faster absorbtion rate from the subcutaneous injection site and a shorter duration of action compared to soluble human insulin (Holleman and Hoekstra, 1997) (*Figure 2, Table 2*).

This rapid action of lispro that coincides with the postprandial rise in blood glucose has three theoretical advantages:

1. The fast action allows the injection to be given immediately before meals
2. The rapid peak action should reduce postprandial hyperglycaemia

3. The short duration of action could decrease the risk of hypoglycaemia between meals and at night time as there is less overlap with the basal insulin.

Insulin lispro has been available for clinical experimental use as short-acting insulin for around 5 years, and has been available on prescription in the UK for 2 years. There is now extensive clinical experience, mostly in patients with type 1 diabetes, with lispro as part of a basal bolus regimen along with isophane insulin injected around 10 pm (Koivisto, 1998).

Studies have consistently shown a reduction in postprandial blood glucose, with no overall effect on HbA1c (*Table 3*). In patients with type 1 diabetes the rate of mild hypoglycaemia was significantly reduced (Anderson et al, 1997a) and similar reductions in mild hypoglycaemia were seen in patients with type 2 diabetes (Anderson et al, 1997b). A meta-analysis of eight trials showed a reduction in severe hypoglycaemia (coma or requiring treatment with glucagon or intravenous glucose) in patients with type 1 diabetes (Brunelle et al, 1998), but severe hypoglycaemia is a rare occurrence in patients with type 2 diabetes (Heller, 1993).

As a result of the shorter duration of action the need for snacks between meals should be reduced, and anecdotal evidence suggests that this may be the case, but definitive evidence is awaited. When patients with type 1 diabetes were questioned about their treatment the satisfaction scores were significantly higher for insulin lispro than for human soluble insulin. The main reason for the increased satisfaction was the greater convenience of lispro which can be injected immediately before meals (Kotsanos et al, 1997).

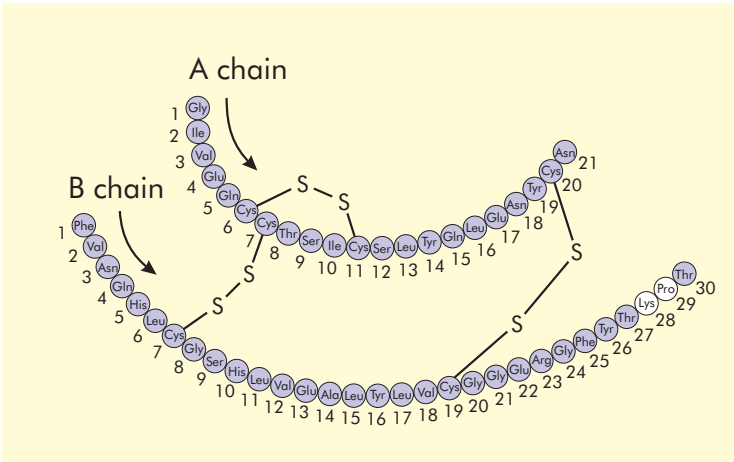

Figure 1. Structure of insulin lispro. Human insulin is converted to lispro by switching the order of two amino acids (proline and lysine) in the insulin B-chain positions 28 and 29 to lysine and proline (from Koivisto, 1998).

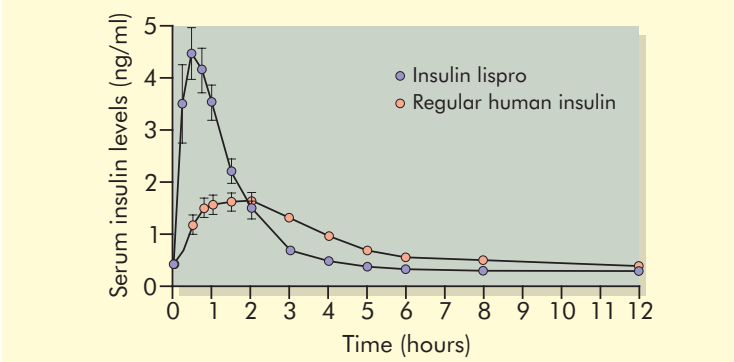

Figure 2. Serum insulin concentrations after a subcutaneous injection of insulin lispro and human soluble insulin. Insulin concentrations peak faster and higher and decrease more rapidly after the injection of insulin lispro as compared to human insulin (from Koivisto, 1998).

TABLE 2.
Pharmacokinetics of lispro insulin

Faster onset of action
Higher peak
Shorter duration of action
Less variation in action depending on the site of injection than soluble (regular) insulin

OTHER INSULIN REGIMENS

Several other insulin regimens are used for patients with type 2 diabetes (*Table 4*). The commonest insulin regimen in routine practice in the UK is the use of a premixed formulation of short- and intermediate-acting isophane (NPH) insulin injected 20–30 minutes before breakfast and the evening meal. When lispro insulin and isophane insulin are in prolonged contact some of the lispro insulin is exchanged with human insulin bound to protamine within the isophane, resulting in a mixture of free and protamine-bound human and lispro insulins.

To avoid this problem neutral protamine lispro (NPL) was developed. This has recently become

TABLE 3.
Clinical advantages of lispro insulin

Can be injected immediately before meals
Reduces postprandial hyperglycaemia
Less hypoglycaemia
Reduces need for snacks between meals
More convenient for patients

available for clinical use as a premixed formulation consisting of 25% lispro and 75% NPL, called Humalog Mix25 (Eli Lilly and Co Ltd, Basingstoke) (Heise et al, 1998). When injected before a test meal in patients with type 2 diabetes the peak rise in blood glucose was lower than a comparable 30/70 mixture (Koivisto et al, 1999) (*Figure 3*).

HUMALOG MIX25 IN CLINICAL PRACTICE

Clinical experience of Humalog Mix25 is limited at present. In one study of 89 patients with type 2 diabetes there was a significant reduction in postprandial hyperglycaemia when comparisons were made between Humalog Mix25 injected immediately before meals and a conventional 30/70 formulation injected at the usual time (Roach et al, 1999) (*Figure 4*). No differences were seen in the HbA1c or the rate of hypoglycaemia, which was low overall. Other preliminary studies have suggested a reduction in nocturnal hypoglycaemia, but this remains to be confirmed.

COMBINATION THERAPY

In the UKPDS patients treated with insulin gained an average of 4 kg. A small study from Finland of patients who had failed on oral agents demonstrated that the same improvement in glycaemic control could be obtained using four injections of insulin daily, two injections daily, or insulin combined with sulphonylureas, but that the latter group required much smaller doses of insulin, and had a smaller weight gain (Yki-Jarvinen et al, 1992). Several studies have confirmed that this is a useful therapy in routine clinical practice (Raskin, 1992; Pugh et al, 1992; Chow et al, 1995).

In obese patients the combination of insulin with metformin leads to better glycaemic control with less weight gain (Yki-Jarvinen et al, 1999).

TABLE 4.
Insulin regimens for type 2 diabetes

UKPDS	Once-daily ultratard insulin
	Basal bolus
Others	'Combination therapy' — oral agents and once-daily isophane
	Twice-daily isophane insulin
	Twice-daily fixed mixtures of soluble and isophane
	Twice-daily fixed mixtures of insulin lispro and insulin lispro protamine suspension

UKPDS = UK Prospective Diabetes Study

PRACTICAL CONSIDERATIONS

The combination of insulin and sulphonylureas is a useful first step in patients with type 2 diabetes if they are not controlled on oral agents alone. Patients are initially educated to inject a small dose of isophane insulin, e.g. 4 units of Humulin I in the morning. Once they are familiar with the technique of injection the time of injection is switched to the evening and the dose

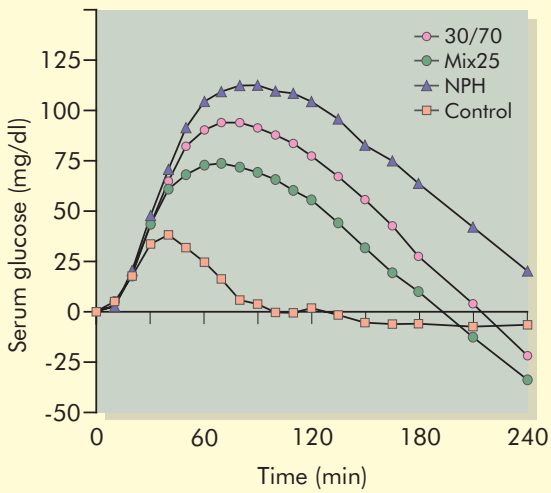

Figure 3. Rise in blood glucose after a test meal in health control subjects and patients with type 2 diabetes after the injection of Humalog Mix25, premixed 30% soluble 70% isophane (30/70), and isophane (NPH) insulin (from Koivisto et al, 1999).

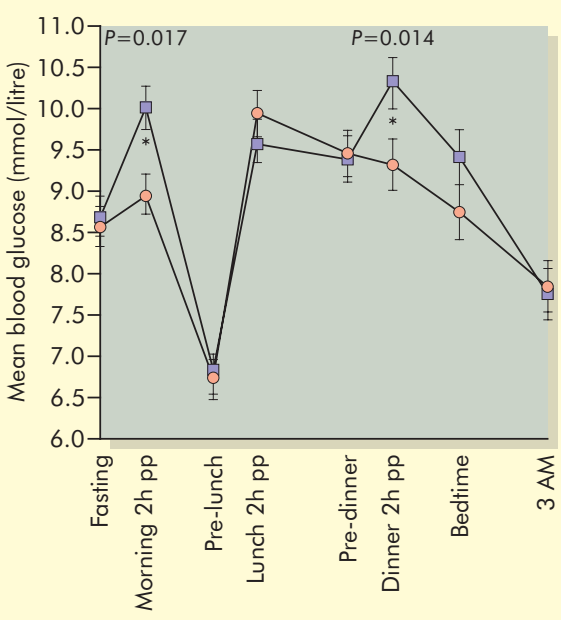

Figure 4. Mean blood glucose concentrations from self-monitored eight-point blood glucose profiles for human insulin 30/70 (squares) and Humalog Mix25 (circles). Error bars represent standard error of the mean (SEM) (from Roach et al, 1999). pp = postprandial.

is slowly increased over a period of weeks, with a target fasting blood glucose of 6 mmol/litre. If the dose exceeds 40 units, or if the blood glucose in the second half of the day cannot be controlled without hypoglycaemia in the morning, then the patient is switched to twice daily Humalog Mix25 with two thirds of the total daily dose injected in the morning immediately before breakfast and one third injected before the evening meal.

FUTURE PROSPECTS

There will be a wider range of insulin analogues available in the near future for the treatment of type 1 and type 2 diabetes. A second rapid acting insulin analogue (Novorapid, Insulin Aspart from Novo Nordisk Pharmaceuticals Limited, Crawley), which seems very similar in action to lispro, is now available for use in basal bolus regimens, and fixed mixtures should be available within the next few years. There are also several companies who are developing intermediate and long-acting analogues that have flatter time-action profiles. These are for use as background insulins, and will hopefully cause less nocturnal hypoglycaemia. The first of these (HOE 901, Hoechst Marion Roussel Ltd, Denham) should be available shortly for use in the UK. HM

Conflict of interest. Dr Fisher is a member of the Humalog Mix25 Study Group, and has advised Eli Lilly on the marketing of analogue insulins in the UK. He was supported as a research registrar by a grant from Eli Lilly.

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KEY POINTS

- Tight glycaemic control of type 2 diabetes can prevent microvascular complications of diabetes.
- Currently available oral agents are unlikely to control patients long-term, and if blood glucose targets are not reached then patients should be converted to insulin therapy at an early stage.
- Many different insulin regimens are available, including combining oral agents with insulin, and the regimen can be tailored to the needs of the individual patient.
- Newly available mixtures of insulin lispro and insulin lispro protamine suspension are more convenient for patients, reduce postprandial hyperglycaemia, and may cause fewer problems with hypoglycaemia.