Insulin delivery devices

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ABSTRACT Insulin therapy remains the cornerstone of treating patients with diabetes mellitus. All patients with Type 1, and many with Type 2, diabetes are treated with insulin. This article describes the discovery and evolution of insulin preparations and discusses current analogue, standard human and animal insulin preparations available for prescription in the UK, highlighting the advantages and disadvantages of the various preparations. An overview of initiating insulin therapy and typical insulin doses and regimes is given. To update general physicians, the necessary adjustments of insulin therapy for intercurrent illness are briefly considered. There is an array of different insulin delivery devices for subcutaneous insulin injection, which can be confusing, and the general advantages and disadvantages of such devices are examined. Recent insulin delivery device advances include the modern continuous subcutaneous insulin infusion devices or external insulin pumps. Advances in this field are rapid and strive towards the development of a closed loop insulin delivery device. Continuous subcutaneous insulin infusion devices are discussed along with the existing guidelines for their use in the UK. Currently continuous subcutaneous insulin infusion therapy is more widely used in other countries compared with the UK. Finally, future possible methods and routes of insulin delivery are reviewed, including inhaled, closed loop pump or oral.

KEYWORDS Analogue insulin, continuous subcutaneous insulin infusion (CSII), diabetes mellitus, insulin

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EDUCATION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease that results in the permanent destruction of the insulin-producing beta cells of the pancreas. Type 1 diabetes mellitus can therefore be thought of as an absolute deficiency of insulin and is uniformly fatal unless treated with exogenous insulin. In contrast, Type 2 diabetes mellitus (T2DM) is a metabolic disorder resulting from a relative deficiency of insulin and insulin resistance. All patients with T1DM and more than 60% of patients with T2DM of 10 years' duration will require insulin therapy to maintain adequate glycaemic control.

## DISCOVERY OF INSULIN AND KEY DEVELOPMENTS IN PREPARATIONS

Frederick Banting and Charles Best (while working for Professor John Macleod) isolated a canine pancreatic extract called 'isletin' and subsequently showed that blood glucose levels would be lowered if the extract was injected into pancreatectomised dogs. James Collip subsequently purified the extract for human injection (insulin). In 1922 Leonard Thompson was the first human to be given bovine insulin; however, impurities in the insulin often resulted in localised reactions and differing concentrations led to unpredictable hypoglycaemic attacks. In 1923 Banting and Macleod were awarded the Nobel Prize in Medicine, shared with Best and Collip.

In the 1940s and 1950s insulin with prolonged duration of action was developed, i.e. soluble insulin suspended with protamine (neutral protamine Hagedorn (NPH) preparations) or zinc (Lente insulin preparations).

Improved purification in the 1970s helped to reduce the immunogenicity of animal insulin preparations. In the 1980s, genetic engineering allowed the biosynthesis of recombinant human insulin. From the 1990s onwards, insulin analogues have come to the market. Analogue insulin has had the human insulin molecule modified (i.e. changing the amino acid structure) to improve the pharmacokinetics of the preparation.

CURRENT INSULIN PREPARATIONS

In the UK, insulin is only available in U100 concentration (100 units per millilitre). The majority of patients in the UK use recombinant human insulin or human analogue insulin. However, some patients find that switching to recombinant human insulin destabilises their control and therefore continue to use animal insulin to achieve satisfactory glycaemic control. The action of injected insulin should mimic the normal secretion of insulin. There should be a low background level with sharp increases in insulin concentration after food ingestion.

Soluble insulin, when injected subcutaneously, forms hexamers, i.e. six insulin molecules associate together thus delaying absorption. This gives a peak onset of action two hours after the injection and lasts six to eight hours. Typically, blood glucose peaks one to one-and-a-
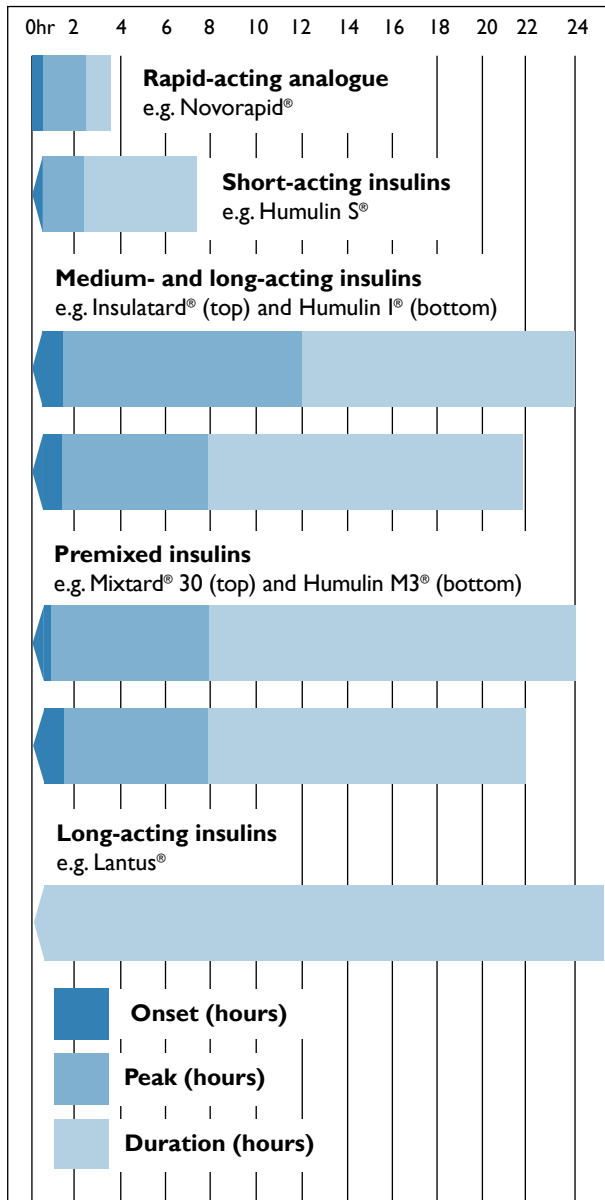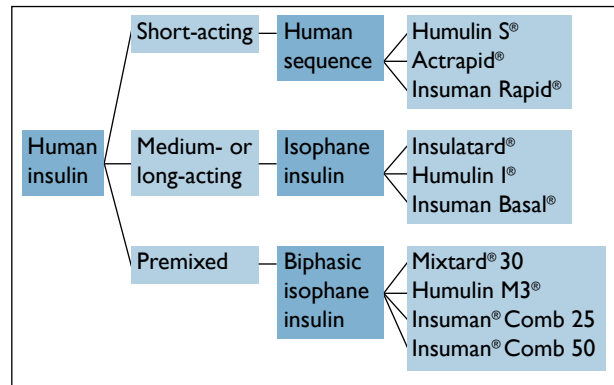
FIGURE 1 Diagram illustrating time to onset, peak and duration of action of various insulin preparations.

FIGURE 2 Human insulin.

FIGURE 3 Analogue (human) insulin.

FIGURE 4 Animal insulin.
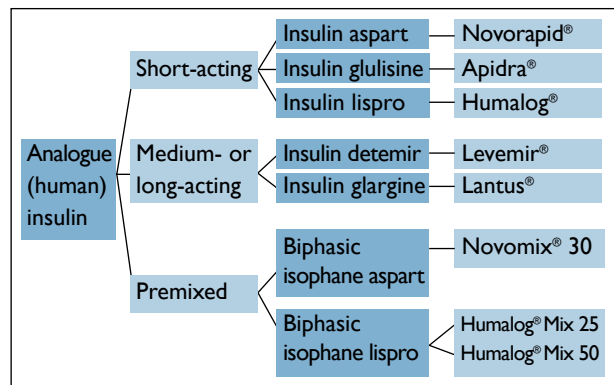
EDUCATION

half hours after food and glucose levels return to basal within three to four hours. Hence there is a mismatch between soluble insulin action and blood glucose levels.

With rapid-acting insulin, changes to the amino acid structure reduce the extent of association of hexamers. This form achieves peak onset of action one to one-and-a-half hours after injection, hence patients may inject just before, during or even after meals. This allows adjustment of insulin doses according to portion size eaten.
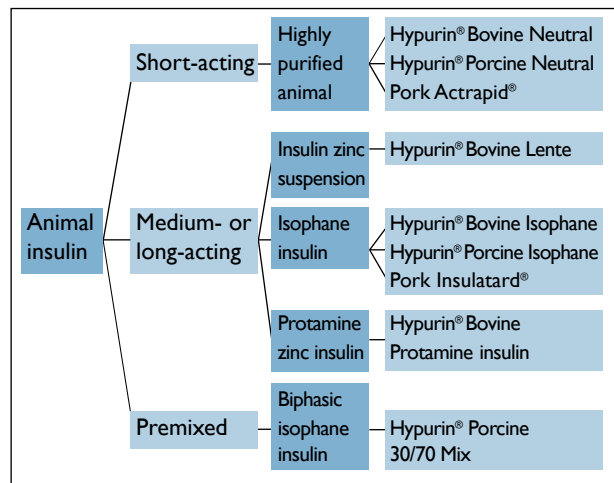
Human isophane (NPH) or zinc insulin preparations do not provide constant basal insulin levels following a single daily injection. They have a peak in their action usually six to eight hours after injection which can lead to hypoglycaemia. Their duration of action is usually between 12–18 hours and they need to be resuspended

(to ensure adequate mixing) before injection, or the absorption of the insulin from the subcutaneous tissue can be erratic.

Long-acting analogues provide better constant background rates of insulin release from subcutaneous tissues. Insulin glargine (Lantus®) has an altered amino acid structure resulting in an acidic preparation which precipitates in the subcutaneous tissue, producing an insulin depot that gradually releases insulin over approximately 24 hours. Insulin detemir (Levemir®) has

TABLE 1 Criteria for immediate commencement of insulin therapy

Significant weight loss secondary to poor glycaemic control
Ketonuria
Hyperglycaemic symptoms causing considerable distress
Co-morbidity dictates that rapid tight glycaemic control would be advisable

TABLE 2 Insulin regimens and suggested suitability criteria

Once-daily basal injections	Given same time each day, often before bed	May suit patients who have partial insulin deficiency (i.e. patients with T2DM) in combination with oral agents. Insulins suitable for this regimen include long-acting analogue or isophane (NPH) insulins.
Twice-daily mixtures	Given before breakfast and evening meal	These can be used in T1DM patients who are unable to cope with a basal bolus regimen or T2DM patients who are inadequately controlled by the once-daily basal injection.
Basal-bolus	Short-acting insulin before meals and long-acting insulin before bed	This is the regimen of choice for patients with T1DM. It is more flexible and allows a better mimicry of the physiological pattern of insulin concentrations.

a fatty acid side chain added, which delays the action of the insulin by facilitating the self-association of two insulin molecules and the reversible binding to albumin. Both rapid- and long-acting analogue insulins have a less proven track record in pregnancy.

Premixed combinations of short-acting and longer-acting insulin are known as biphasic insulins. In the UK, the number refers to the percentage of short-acting insulin, e.g. Mixtard® 30 contains 30% short-acting insulin with 70% long-acting insulin. Figure 1 summarises the profile of action of different insulin preparations and Figures 2, 3 and 4 illustrate the various different insulin preparations available: human, analogue and animal insulin, respectively.

INSULIN INITIATION

All patients with T1DM require urgent insulin treatment, usually starting the same day as the diagnosis is made. The typical total daily dose is 0.4–1.0 units/kg, given as two or more divided doses (see Table 1).

Many patients with T2DM will require insulin therapy. An appropriate starting total daily dose for such patients may be 0.2 units/kg, as basal insulin only, but individual

TABLE 3 The 'sick day rules'

Insulin should never be stopped as blood glucose may be higher than normal despite a reduction in oral intake.
Blood sugars should be checked more frequently than usual, e.g. every two to four hours.
To prevent dehydration, drink plenty of non-sugary drinks.
Additional insulin should be given if blood sugars are high, to bring down readings and suppress ketone production.
Urine should be tested for ketones if feeling unwell or sugars are greater than 14 mmol/L.
Very occasionally sugars will fall, treat hypos in the normal way.
Contact your family doctor or diabetes team urgently if concerned.

clinical practice will vary. Commencing insulin involves multidisciplinary care, including dietetic and diabetes specialist nurse review.

INSULIN REGIMENS

The aim of administering insulin is to match the body's physiological insulin action. Typical regimes shown in Table 2 achieve this with varying degrees of success.

Optimising control and insulin dose adjustment

It is important to review blood glucose readings, food intake, activity levels and the possibility of intercurrent illness for at least the preceding 48–72 hours when considering insulin dose adjustment. Premeal blood glucose targets for optimal control should be in the range 5–7 mmol/L for most patients and there should not be a significant drop (i.e. >3 mmol/L) in blood glucose levels overnight. If blood glucose readings are repeatedly outside the target range at a given time then the insulin dose acting at that time should be adjusted by 10–20% (see insulin time profiles in Figure 1 to understand which insulin to adjust). For example, if a patient is on a basal bolus regime, using Lantus® 20 units once daily prebed and Novorapid® 6–10 units premeals, and experiences mild recurrent hypos at 8.30 pm, then the Novorapid® dose prior to the evening meal should be decreased by 1–2 units. The avoidance of hypogly-caemia is important, and for some patients with poor warning symptoms it may not be possible to achieve the suggested glucose targets safely, thus higher targets for such individuals should be agreed.

If intercurrent illness is present and blood glucose readings are above 14 mmol/L, it is important to test for ketones. If ketones are present, expect to increase the insulin doses significantly above the previous guidelines, i.e. 10–20% of the total daily dose may be needed every two hours. This should be given as soluble or fast-acting analogue insulin, to clear ketones and to bring glucose readings back to target.

TABLE 4 Side effects of subcutaneous insulin injections

Hypoglycaemia
Weight gain
Peripheral oedema (short term)
Bruising at injection sites
Lipohypertrophy (lumps)
Lipoatrophy (subcutaneous fat loss)

'SICK DAY RULES'

Each patient who is prescribed insulin should be aware of actions to take if unwell. These are known as the 'sick day rules' and are summarised in Table 3.

INSULIN DELIVERY

The majority of insulin is administered by subcutaneous injection; Table 4 summarises the potential side effects.

Insulin pen devices

Developed by John Ireland in 1981 based on a fountain pen, insulin pen devices are now available as reusable (refillable pen with new insulin cartridge) or disposable (whole pen device thrown away once the integrated insulin cartridge is empty) devices. Most devices have a manual dose dial on the opposite end from the needle, allowing quick and easy dose-setting. Maximal single dose varies from 40–80 units in 0.5–2.0 unit increments. The needles for pen devices are very fine and come in several lengths; generally 5–8 mm length is recommended. A new needle should be used for each injection.

SQ-PEN is a needle-free insulin delivery device for use with 3-ml refillable pen devices. Doses can be adjusted in one unit increments. It is not pain free, is considerably more expensive than standard pen devices and should be reserved for patients with genuine needle phobias.

In summary, pen devices are convenient and discrete. They are more expensive than syringes and do not permit free mixing of insulin.

Syringe and needle

Disposable syringes with needles are available in 0.5 and 1 ml volumes, with dose increments marked in units of insulin. They are cheaper than pen devices and allow free mixing of soluble and isophane insulin doses to be administered as a single injection. They require good manual dexterity to draw up insulin doses accurately.

Insulin delivery devices with large dials

These are disposable insulin devices with large dials (e.g. InnoLet®) for patients with visual impairment or reduced manual dexterity, e.g. arthritic hands.

Inhaled insulin

Inhaled insulin (Exubera®) was initially licensed in the UK in 2006 for patients with evidence of poor glycaemic control and a true needle phobia or persistent problems with injection sites. In October 2007 Exubera® was withdrawn due to low market demand. Other companies have since abandoned development of alternative inhaled insulins.

The long-term safety of inhaled insulin has not been established.

Continuous subcutaneous insulin infusion devices (external insulin pumps)

Continuous subcutaneous insulin infusion (CSII) devices comprise an external programmable pump and insulin reservoir to which the patient is continuously connected by means of a subcutaneous cannula. Arguably they are the most flexible method of insulin administration currently available. The insulin reservoir is usually filled with a rapid-acting insulin analogue, e.g. Humalog®. The CSII device is preprogrammed to deliver basal insulin at varying rates throughout a 24-hour period; many patients will have three or four different basal rates within a 24-hour period.

Patients initiate mealtime bolus insulin doses by pressing the corresponding buttons on the CSII device. Dose increments for most devices are 0.05–0.1 unit of insulin. Most modern pumps have software that helps patients to calculate the appropriate bolus dose depending on their current blood glucose level, when their last bolus dose was and what carbohydrate is going to be eaten.

Evidence has shown that for patients with T1DM, CSII therapy results in:
- a reduction in HbA1c;
- an improvement in quality of life; and
- a reduction in the incidence of severe hypoglycaemia.

At present only 1–2% of UK patients with T1DM use CSII devices, compared with 20–30% in other countries. The updated NICE guidelines (2008) recommend CSII therapy for T1DM patients with disabling hypoglycaemia (repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life) or those unable to achieve HbA1c <8.5% despite a high level of self care on an appropriate insulin regimen.

Trials to date have been less conclusive for T2DM, and NICE currently does not recommend CSII therapy for patients with T2DM.

CSII therapy should be initiated and supported by a specialist team.

EDUCATION

FUTURE METHODS

The following methods of insulin delivery are currently at various stages of development:

Closed loop insulin pumps. These involve the pump device self-monitoring blood or interstitial fluid glucose concentrations and adjusting the insulin infusion rate accordingly, thus requiring little input from the patient. Continuous glucose monitoring would allow near instantaneous adjustment of the insulin infusion rate. This technological solution would constitute an artificial pancreas. At present the accuracy of continuous glucose monitoring systems has limited progress.

Oral insulin. A device similar to a metered-dose inhaler used for asthma has been developed to administer insulin as a fine mist spray to the oral cavity. This allows absorption by the buccal mucosa. The product, Oral-lyn®, has been submitted for marketing and sale in Canada and is currently undergoing phase III trials in Italy. Poor absorption of insulin from the gut and unpredictable transit times have hampered attempts to deliver oral insulin directly to the liver by absorption into the portal venous system.

Intranasal insulin. Development has been hampered by low bioavailability and unpredictable absorption, probably secondary to nasal mucus production.

Insulin patches. These have been attempted in various forms with little success.

KEY POINTS

- Careful assessment is required by the multidisciplinary team when commencing patients on insulin therapy, and insulin regimens must be tailored to the individual patient's requirements.
- Patients should be aware of the necessary actions to take when unwell – the 'sick day rules'.
- Subcutaneous injection using a variety of pen devices remains the most popular means of administering insulin.
- Human insulin analogue preparations allow a more accurate mimicry of physiological insulin action compared with soluble insulin and NPH preparations.
- Currently available continuous subcutaneous insulin infusion devices (external insulin pumps) are the technology that allows the most flexible delivery of subcutaneous insulin.

FURTHER READING

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