Glycaemic control with advanced new insulins for the treatment of diabetes

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Summary

The benefits of maintaining blood glucose levels as near normal as possible are well appreciated. The advent of insulins with varying rates of onset and duration of action has made it possible to closely mimic normal physiological glycaemic control.

This review considers advances in insulin therapy with attention focussed on the most recently introduced rapid-acting insulin analogue glulisine (Apidra®) and the novel inhaled insulin Exubera®.

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Key words

Insulin; Exubera; analogues; diabetes

Introduction

Current guidelines and targets for the management of diabetes emphasise the importance of achieving optimal glycaemic control to reduce the vascular morbidity and mortality associated with diabetes. The Diabetes Control and Complications Trial (DCCT) and the UKPDS (United Kingdom Prospective Diabetes Study) demonstrated the importance of maintaining glycaemic control as near normal as possible in type 1 and type 2 diabetes respectively.[1,2]

Tighter glycaemic targets have resulted in the earlier introduction of insulin therapy in type 2 diabetes and the intensification of insulin treatment in type 1 and type 2 diabetes. The recent American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) consensus algorithm advises on the introduction and intensification of insulin treatment and recommends the use of metformin (and a thiazolidinedione where licensed) with insulin in the management of type 2 diabetes.[3]

Insulin therapy attempts to mimic the normal insulin response and typically comprises a long-acting (basal) component supplemented with a shorter-acting (bolus) insulin before meals.[4,5] The availability of pre-mixed (biphasic) insulin preparations provides a practical compromise for those who require more intensive treatment but are unsuited to a basal-bolus protocol. This article is focused on recently available insulin preparations and consideration is given to possible future insulins.

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Evolution of insulin preparations

In the early days of insulin therapy, insulin was extracted from the pancreas of dead cattle and pigs and incompletely purified (Table 1). This often caused allergies and the formation of insulin antibodies which resulted in patients needing very high insulin dosages. However the situation improved with the advent of the highly purified 'monocomponent' insulins. The emergence of DNA technology saw the commercial production of semisynthetic (enzymatically modified porcine insulin), and biosynthetic human insulins (Table 2), which lacked the immunological problems associated with bovine and porcine insulins. Biosynthetic human insulins are currently the mainstay of insulin therapies.

As well as reduced immunogenicity, advances have been made in altering the duration of action of insulins. The addition of protamine (a fish sperm protein), and use of a zinc suspension extend the duration of action of insulin, for example neutral protamine Hagedorn (NPH)/isophane and lente insulins respectively. Premixed 'biphasic' insulin preparations have been available for decades and the range expands with the diversity of insulins. It is perhaps worth noting that the European custom of stating the proportion of the shorter:longer acting insulin is not an international approach – in the USA the proportion of longer:shorter acting insulin is stated – although biphasic insulin preparations are increasingly including the proportion of shorter-acting insulin in the trade name.

Decade	Available for clinical use
1920s	Insulin introduced (1st clinical use 1922) Extraction of bovine and porcine insulins (short-acting)
1930s	Improved purification
1940s	NPH introduced (longer-acting)
1950s	Lente and ultralente insulins (longer-acting)
1970s	Monocomponent insulins (highly purified)
1980s	Premixed biphasic insulins Biosynthetic human insulins Pen injector devices Pumps for CSII
1990s	Rapid acting analogues of human insulin
2000s	Long-acting analogues of human insulin Exubera – inhaled insulin (short-acting)

Table 1. Evolution of insulin therapy[4,5]

The duration of action of insulin has been further refined with the emergence of analogues of human insulin. The new rapid-acting analogues, insulin aspart (NovoRapid®) and insulin lispro (Humalog®) have been structurally modified so that they have a high concentration of insulin molecules in the monomeric state, allowing them to be quickly absorbed into the circulation.[6,7] They have a rapid onset and short duration of action, making them particularly useful to reduce postprandial glucose excursions. Their use in children is only recommended if there are benefits compared with use of a non-analogue, short-acting (soluble/neutral) insulin. Biphasic preparations are also available.

The modifications of human insulin in the long-acting analogues, insulin glargine (Lantus®) and insulin detemir (Levemir®), result in slow dissociation to the monomeric form. This provides a gradual, relatively constant availability of insulin in the circulation, which acts as a basal insulin supply. These insulins are suitable for once daily (glargine) or twice daily (detemir) injection in basal-bolus regimens, but their use is not approved in children ≤6 years of age.

Delivery devices

Insulin delivery devices have also changed over the decades with needles and syringes decreasing in size, becoming disposable and these technologies then being refined to produce pen injection devices which may be pre-filled, have cartridge refills and dose dialling options, making injecting simpler and less susceptible to user error.[6] Needle-free devices such as the Vitajet, J-Tip and the mhi-500 are available in the UK, but usage has been limited as only small amounts of insulin can be delivered.[8]

Using increasingly complicated engineering, continuous subcutaneous insulin infusion (CSII) has made pump usage more reliable and user-friendly. However not all delivery devices are suited to all insulins, with some insulin cartridges only being manufactured to fit specific 'pens' and some insulins not being recommended for use in CSII pumps, e.g. Actrapid®, because it may block the catheter or needle.

The most recent additions to the insulin armamentarium are the rapid-acting insulin analogue glulisine (Apidra) and the inhaled insulin system (Exubera).

Glulisine

Rapid-acting insulin analogues are taken shortly before (10–15 minutes) or during a meal and appear in the circulation within about ten minutes. They have a duration of action of 3–4 hours with peak activity occurring within 1–2 hours (lispro) and 1–3 hours (aspart) of administration.[4]

In 2004 glulisine was licensed in Europe for the treatment of adults with type 1 and type 2 diabetes, but it was not launched until September 2005. It is a rapid-acting analogue of human insulin in which two amino acids have been substituted to increase the rate of insulin absorption. Glulisine absorption is similar to, or possibly slightly faster than, aspart and lispro.

Glulisine has a rapid onset of action (approximately 10 minutes), a peak action of 1–2 hours and duration of action of about 3–4 hours. It should normally be used in regimens that include a basal insulin preparation or in association with oral antidiabetic agents in some patients with type 2 diabetes. If glulisine is being mixed with NPH human insulin it is important that the glulisine is drawn into the syringe first and the injection made immediately after mixing. Glulisine should not be mixed with any other insulin.[9]

Glulisine is equipotent to human insulin and should be

administered shortly before (0–15 minutes) or soon after (within 20 minutes) a meal. It is supplied as a standard clear, colourless solution at 100 units/ml (U-100) in 10 ml vials for use with insulin syringes and CSII pumps; as 3 ml cartridges for use with pen injectors such as OptiPen®, or as a pre-filled Optiset pen containing 3 ml of solution for injection. This insulin should be stored in a refrigerator at 2–8^{0}C (36–46^{0}F) and protected from light; it should be discarded if frozen. Opened vials or cartridges should be discarded after 28 days whether kept refrigerated or not. The pen injector – with or without cartridge system – should not be stored in a refrigerator.

Insulin cartridges are normally removed from the refrigerator 1–2 hours before use. Infusion sets and the glulisine reservoir should be discarded if exposed to temperatures >37^{0}C (98.6^{0}F) or after a maximum of 48 hours of use. When using a pump system, glulisine cannot be mixed with any other insulin.

Due to inadequate data, glulisine is not recommended for use during pregnancy and it is unknown whether glulisine passes into the milk during lactation. In clinical trials some glulisine-treated patients experienced injection site and local hypersensitivity reactions, but these generally resolved as treatment continued and treatment emergent adverse events were not significantly different between patients treated with glulisine and regular human insulin.

Inhaled insulin

The lungs offer a large surface area (>100 m^2) with a thin highly vascularised epithelium for the absorption of insulin into the capillary circulation. This allows an onset of action at least as fast as that observed with subcutaneous injections of rapid-acting insulin analogues.[7,10]

Use of recombinant DNA technology for:

Separate synthesis of insulin A and B chains in *Escherichia coli* which are recombined:
- crb – chain recombinant bacterial (e.g. Insuman®)

OR

Insertion of the proinsulin gene into a single organism:
- prb – proinsulin recombinant bacterial; uses *Escherichia coli* (e.g. Humulin®)

OR
- pyr – proinsulin yeast recombinant; uses *Saccharomyces cerevisiae* (e.g. Actrapid)

Table 2. Summary of production of biosynthetic human insulin

Generally about 15% of the insulin delivered via an inhaler actually enters the bloodstream, although the proportion of insulin dosage inhaled can vary between 15–30% from dose to dose in the same person. However, such variation can also be observed using rapid-acting analogue or human insulin injections. Inhaled insulin has a lower bioavailability (approximately 10–15%) than subcutaneous insulin, which is mainly due to losses in the upper airways. Efforts are being made to reduce this insulin wastage.

Specialist insulin formulations suitable for inhalation and smaller improved delivery systems have propelled this approach from bench to bedside. Several inhaled insulin systems are in the later stages of development (Table 3). Exubera was approved by the regulatory authorities in the USA and Europe in January 2006 and was the first inhaled insulin system to reach the market, with its UK launch in May 2006.

Exubera

Exubera is the result of a partnership that now only involves Nektar Therapeutics and Pfizer Inc. Nektar pioneered and developed the core technologies including the formulation and particle engineering for the insulin powder, the filling and packaging techniques for the insulin blister and the Exubera Inhaler with its components. Nektar supports manufacturing by insulin powder processing and production of the inhaler and Pfizer manufactures and sells Exubera.

Exubera insulin is a powdered formulation of human insulin which has been produced by recombinant DNA technology using the bacterium *Escherichia coli*. The insulin is supplied in 1 mg and 3 mg unit dose blisters, dispensed via a specialised oral inhalation device that weighs about 4 ounces and when closed is about the size of a spectacle case.

Following insertion of an Exubera blister into the inhaler, the handle is pumped and on pressing a button the blister is pierced and the contents are dispersed into the chamber. The aerosolised powder particles, which are about 5 µm in diameter, should be inhaled from the mouthpiece in one long slow inhalation and the breath held for five seconds, to allow the insulin to penetrate deep into the lungs, followed by normal exhalation. Only about 40% of the insulin from the blister reaches the deep lung, while 30% remains in the blister or inhaler. Thus the patient should employ a routine technique to

System	Company	Development
Exubera	Pfizer + Nektar	In clinical use
AERx® Aerodose®	Novo Nordisk + Aradigm, Disetronic + Aerogen Kos Pharmaceuticals	Phase III Phase II? Phase II
TI	MannKind Biopharmaceuticals	Phase III
AIR®	Eli Lilly + Alkermes	Phase III

Table 3. Inhaled insulin systems[7,10,11]

ensure optimal and consistent drug delivery.

The dose equivalents of the predispensed tear-off blisters are: 1 mg dose blister approximately 3 IUnits and 3 mg dose blister approximately equivalent to 8 IUnits of regular subcutaneous insulin respectively. Consecutive inhalation of three 1 mg dose blisters should not be substituted for a 3 mg dose blister, since the circulatory availability after three 1 mg blister doses is 30–40% greater than after inhalation of a 3 mg blister dose.

To help avoid blister confusion the 1 mg blister is labelled in green ink and the card spine has a raised ridge, whilst the 3 mg blister uses blue ink and there are three raised ridges on the spine of the card – this is especially helpful if a combination of dose blisters is required. The packs should be stored at room temperature (15–30^{0}C, 59–86^{0}F) within the foil pouch and should be used within three months of opening the pouch. The pouch contains a desiccant as it is important to protect the blisters from moisture. The blisters should be stored at 25^{0}C, not in a refrigerator and should be discarded if they have been frozen.

The Exubera inhaler should be stored and used in a dry environment. It can be used for up to one year, but the release units should be changed every two weeks and therefore they are supplied with some insulin blister packs.[12,13]

Exubera has been approved for the treatment of adults with type 2 diabetes requiring insulin therapy (± oral agents) and in addition to long- or intermediate-acting subcutaneous insulin in adult patients with type 1 diabetes for whom the potential benefits of inhaled insulin outweigh potential safety concerns. There are no apparent differences in the pharmacokinetic properties of Exubera when comparing younger adults with patients >65 years.

Studies comparing Exubera, rapid-acting analogues and regular human insulin have demonstrated that the total glucodynamic effect is similar with all three types of insulin, despite variations in onset and duration of action.[14–16] The fast onset of Exubera action is similar to that of rapid-acting analogue insulin, whereas the longer duration of Exubera action is comparable to regular human insulin. This makes Exubera attractive for the management of meal-related hyperglycaemia, and since it should be administered not more than ten minutes before consuming a meal it is convenient to use with unpredictable mealtimes.

Initial pre-meal doses of Exubera are based on body weight (Table 4) and titrated to optimal dosage in association with blood glucose monitoring. Due to the blister sizes it is unlikely that it will be suitable for people of low body weight requiring very small insulin doses or for patients who require very high insulin doses.[12]

The glucose-lowering efficacy of Exubera, while being comparable to regular subcutaneous insulin therapy, has shown greater reductions in fasting and postprandial glucose levels in some studies.[11] Hypoglycaemia, which is the most common side-effect of insulin therapy, showed a similar incidence with Exubera compared to similar subcutaneous administration regimens. Weight gain among insulin treated patients was also similar. The absorption of Exubera is independent of body mass index, but extra care is needed in people of lower body weight.

Elevated anti-insulin antibodies have been reported, but these have not been associated with clinical consequences or changes in glycaemia. However, the risk of these antibodies to the fetus is unknown, thus Exubera should not be used during pregnancy. Small quantities of insulin may be present in breast milk, but studies with inhaled insulin have not been conducted during lactation.

In clinical trials about a quarter of patients reported mild-to-moderate cough within seconds or minutes of inhaling Exubera. The cough was generally non-productive and transient and only 1.2% of patients discontinued treatment. Due to the effect of Exubera on pulmonary function (some patients experienced notable declines which reversed on discontinuation) this should be assessed before, and six months after, commencing therapy and annually thereafter. If a decline from baseline of ≥20% in FEV_1 (forced expiratory volume) is observed and

confirmed, Exubera should be discontinued.

It is not usually necessary to discontinue Exubera during intercurrent respiratory illness. Exubera is not recommended for use in people with asthma, chronic obstructive pulmonary disease (COPD) or underlying lung disease, and extra vigilance is needed in patients who use other inhaled products.

The use of Exubera is contraindicated in patients who smoke or have only discontinued smoking within the six months before commencing therapy. The risk of hypoglycaemia is higher in smokers, especially in the first 2–3 hours after dosing. The rate and extent of absorption of insulin is greatly enhanced (up to five-fold) in smokers, but was reduced in a study in non-smokers with two hours of passive exposure to cigarette smoke. The effects of chronic exposure to passive cigarette smoke have not been investigated.[11,12]

From the patient perspective, compared with subcutaneous insulin, Exubera scores highly in terms of convenience, ease of use, treatment satisfaction and impact on quality of life.[11] Among type 1 and type 2 diabetic patients who have received Exubera the majority chose to remain on this treatment and patients are more likely to accept insulin treatment when inhaled insulin is an option.[17,18]

Exubera appears to be popular with patients and this may enable more people to achieve optimal glycaemic control. However, lack of experience with this method of insulin delivery, associated insulin wastage and a paucity of information on lung pathology with long term exposure may temper the enthusiasm of the healthcare professional to promote its use.

To calculate initial insulin dose, e.g. for a 70 kg patient:					
Body weight (kg) x 0.05 mg/kg = mg rounded down to the nearest whole mg = pre-meal dose				70 kg x 0.05 mg/kg = 3.5 mg = 3 mg	1 x 3 mg blister dose
Body weight kg	**lbs**	**Initial dose/ meal**	**1 mg blister/ dose**	**3 mg blister/ dose**	**Approx regular sc insulin dose IU**
30–39.9	66–87	1 mg	-	3	
40–59.9	88–132	2 mg	2	-	6
60–79.9	133–176	3 mg	-	1	8
80–99.9	177–220	4 mg	1	1	11
100–119.9	221–264	5 mg	2	1	14
120–139.9	265–308	6 mg	-	2	16

Table 4. Guidelines based on body weight for initial pre-meal Exubera dose and approximate equivalent IU dose of regular subcutaneous human insulin[12]

Buccal insulins

Buccal insulin delivery is under investigation by several companies, but the most advanced is the Generex product Oral-lyn® (also known as Oralin® and Oralgen®), which became available in Ecuador in 2005 for the treatment of type 1 and type 2 diabetes. A liquid formulation of regular human insulin is delivered as a fine spray onto the buccal mucosa using a RapidMist® aerosol applicator. The buccal mucosa is highly vascularised which allows for rapid insulin absorption compared to subcutaneous injections. However, the presence of mucus may retard absorption, decrease bioavailability and increase pharmacokinetic variability.

Clinical trial data presented at major diabetes meetings can be viewed on the company website.[19]

Additional approaches

Due to the rapid absorption of insulin across the nasal mucosa it has long been considered a route of administration, although surfactants and absorption enhancers are needed to improve bioavailability. Additionally, the nasal epithelium is susceptible to intercurrent infection and irritation. There has been a resurgence of interest in this route of delivery using powder, liquid and gel formulations, but none is advanced in commercial development.[7]

A transdermal insulin formulation (TMP–02/insulin) is reported to have shown promise in a preclinical study. Research on oral insulin delivery continues and a recent study using a conjugated hexyl-insulin (HIM2) has been encouraging. Formulations to deliver insulin directly to the liver and to provide controlled release of active insulin are also being investigated.[20–22]

Conclusions

Recent decades have seen several advances in insulin preparation and delivery. The availability of long-acting and short-acting insulin analogues has offered genuine opportunities for the implementation of intensive basal-bolus regimens, and the advent of Exubera provides a novel alternative to subcutaneous bolus insulin delivery.

Currently available insulins should help patients to achieve

a more physiological daily glycaemic profile.

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