Recent advances in insulin therapy

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Abstract

Increased attention to good glycaemic control in diabetic patients has encouraged more intensive use of insulin. To help achieve a steady 'basal' insulin supply, a new long-acting insulin analogue glargine (Lantus®) has been introduced. This provides a flatter 'peakless' circulating concentration of insulin than protamine (isophane) and lente insulins, facilitating dose escalation with reduced risk of hypoglycaemia. Another long-acting insulin analogue detemir (Levemir®) is advanced in development. Intensive insulin therapy requires 'top-ups' to coincide with mealtimes. The recently introduced rapid-acting monomeric analogues, lispro and aspart, are particularly useful in this respect. The monomeric analogues are quickly absorbed and short acting: hence they reduce post-prandial glucose excursions (which have been ascribed especial cardiovascular risk) with less risk of hypoglycaemia than conventional short-acting insulin. Premixed rapid-intermediate acting mixtures of monomeric analogues with protamine are also available. Continuous subcutaneous insulin infusion is receiving increased use as the pump technology advances, mainly incorporating the monomeric insulin analogues. Inhaled insulins continue in development, and various oral insulin formulations have entered clinical trials.

Key words: intensive insulin therapy, glargine, detemir, lispro, aspart, inhaled insulin.

Br J Cardiol 2003;**10**:379–83

Introduction

Current guidelines and targets for the management of diabetes mellitus emphasise the importance of intensive treatment regimens to control blood glucose and reduce cardiovascular risk. Ideally, glycaemic control should be as near to normal as practicable for each patient.[1,2] This approach minimises microvascular complications and assists macrovascular protection, forming a crucial part of the overall medication cocktail to address all recognised vascular risk factors in the diabetic patient.

Pursuit of tighter glycaemic targets (table 1) has encouraged earlier introduction of insulin in type 2 patients, and more intensive use of insulin in both type 1 and type 2 patients.[1,3]

Typically, insulin therapy comprises a long-acting basal insulin component supplemented with short-acting insulin to coincide with meals (figure 1). This article is focused on recently available insulin analogues and potential future insulins that may help to mimic more closely the normal daily insulin profile.

Table 1. National Institute for Clinical Excellence (NICE) guidelines 2002 for the management of blood glucose, lipids and blood pressure in patients with type 2 diabetes (www.nice.org.uk Clinical guidelines No 128 and No 167)

Parameter	Target*
HbA_{1C}%	6.5–7.5
Total cholesterol (mmol/L)	< 5
LDL cholesterol (mmol/L)	< 3
Triglyceride (mmol/L)	< 2.3
Blood pressure (mmHg)	< 140/80–< 135/75

Key: *Targets are dependent on co-existent cardiovascular risk, for example as assessed by the Joint British Societies Coronary Risk Prediction Charts, *Heart* 1998;**80**(suppl 2):S1–S29, summarised at the back of the British National Formulary; LDL = low density lipoprotein

Basal insulin analogues

Neutral protamine Hagedorn (also known as NPH; isophane) and ultralente insulins are prone to produce a 'dome-shaped' basal plasma profile. This leaves the patient vulnerable to hypoglycaemia at the peak insulin concentration and hyperglycaemia at the trough. Variability in the rates of absorption of these insulins can also pose difficulties when striving for tighter glycaemic control. Mixing isophane and short-acting insulins, particularly the convenience of premixed ('biphasic') formulations, have much improved the situation but still struggle to achieve good control without 'hypos'.[4,5]

Glargine

The long-acting analogue glargine (figure 2), introduced in August 2002, creates a flatter plasma insulin profile, which more closely matches the basal component of normal insulin release.[6]

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Figure 1. Panels A and B show the normal daily profile of plasma glucose and insulin. Panel C shows the archetype insulin profile expected with a complex regimen involving a single evening injection of a long-acting 'basal' insulin analogue and three injections of a rapid-acting monomeric insulin analogue at meal-times

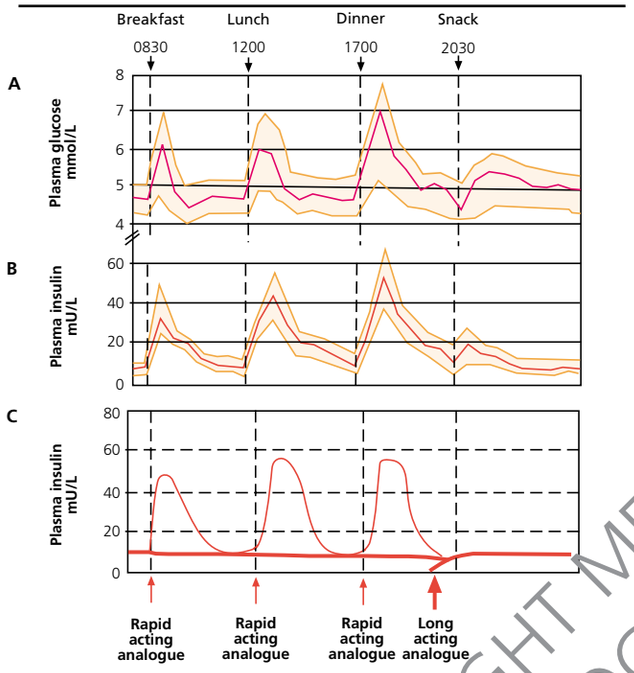


Figure 2. Amino acid sequences of native human insulin, the long-acting analogues glargine and detemir, and the rapid-acting monomeric analogues lispro and aspart. Sequences shown as single letter amino acid code

Glargine (Lantus®) has an isoelectric point close to neutrality, conferring solubility and stability in acid solution within the vial. When injected into the slightly alkaline environment of interstitial fluid, the glargine quickly precipitates and then dissociates gradually providing a constant and ostensibly peak-less 'basal' supply of insulin into the circulation (figure 3). In principle, glargine can be given by once-daily subcutaneous injections at any time of the day, although bedtime is usually preferred. Several studies have reported similar or slightly improved glycaemic control with glargine compared with once- or twice-daily NPH. However, glargine therapy resulted in fewer episodes of nocturnal hypoglycaemia and less weight gain.[7-9]

Detemir

Another long-acting 'basal' insulin analogue is detemir (Levemir®), expected to become available early in 2004 (figure 2). Detemir is insulin linked to a fatty acid (myristic acid). The fatty acid side chain promotes aggregation of detemir in interstitial fluid and delays dissociation and release into the circulation. On entering the blood, the fatty acyl group binds to albumin and a dynamic equilibrium occurs between the free and the albumin-bound forms. Gradual subsequent dissociation from the albumin gives a constant slow rate of release of active monomeric detemir. Studies to-date indicate a predictable effect of detemir on glycaemic control with fewer hypos and less weight gain than NPH.[10,11]

New classification of insulins

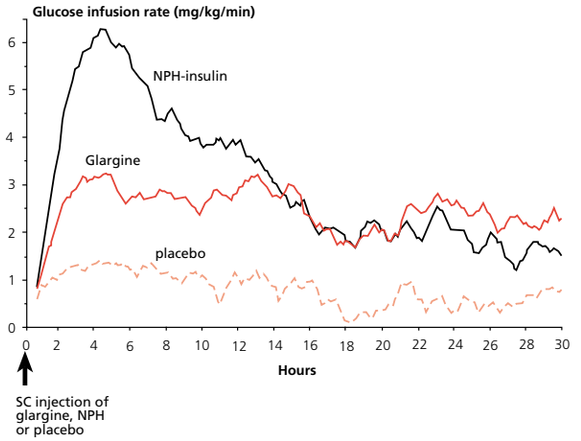
Since glargine and detemir are both clear, soluble, long-acting insulins, it is no longer appropriate to use the old classification of insulins into clear (short-acting) and cloudy (long-acting). A new classification based on speed of onset and duration of action is given in table 2.

Mixing of the new long-acting insulin analogues (glargine and detemir) with rapid-acting or short-acting insulins in the same injection is not recommended due to pH differences which could affect the time-action profile of the insulins.

Meal time insulin analogues

The new rapid-acting insulin analogues lispro[12,13] and aspart[14,15] have quickly established themselves as suited for meal-time injection to boost circulating insulin concentrations to coincide with the period of meal digestion. These insulin analogues (figure 2) are structurally modified to discourage self-association such that

Figure 3. Glucose infusion rate required to maintain euglycaemia after subcutaneous injection of either glargine, NPH-insulin or placebo at time zero. The glucose infusion rate provides an indication of the circulating concentration of insulin, showing an early peak and subsequent trough with NPH-insulin compared with a flatter 'peakless' profile with glargine



Based on data presented by Linkeschowa *et al*. at the European Association for the Study of Diabetes 1999. Published in *Diabetologia* 1999;**42**:(suppl 1); Abstract 880

Table 2. Classification of insulins

Category	Generic type	Examples	Onset of action (mins)	Duration of action (hours)
Rapid		Aspart, lispro	10–20	2–5
Rapid-intermediate		Novomix®, Humalog®	10–20	8–16+
Short	Regular*	Actrapid®, Humulin S®, Insuman Rapid®	15-60	4–8
Short-intermediate	Regular-isophane (NPH) mixture 'Biphasic'	Mixtard®, Humulin M2/3/5®, Insuman Comb®	15–60	8–16+
Intermediate	Isophane (NPH)	Insulatard®, Humulin I®, Insuman Basal®	60–120	8–16+
Long	Crystalline zinc suspensions 'Lente'	Ultratard®, Humulin Zn®	120–240	16–30
Very long		Glargine	60–120	24+

Key: *Regular was previously termed 'soluble', but this is no longer exclusive to short-acting insulins; NPH = neutral protamine Hagedorn

Table 3. Inhaled insulins

Exubera Inhale®	Pfizer, Aventis
AERx Aradigm®	NovoNordisk, iDMS
Alkermes®	Lilly
Aerogen®	Disetronic

they exist at high concentrations in a monomeric state. Consequently they are quickly absorbed into the circulation and have a rapid onset and short duration of action (table 2). This reduces post-prandial glucose excursions and lessens the risk of inter-prandial hypoglycaemia. While requiring patient commitment to several day-time injections, this is compensated by the convenience of injecting just before (or even after starting) a meal, rather than having to anticipate the meal with an injection of short-acting insulin 15–30 minutes in advance.

'Biphasic' premixed formulations of a rapid-acting analogue with protamine have provided a convenient new means to combine mealtime and basal insulin delivery. The biphasic formulation can be given for at least some of the injections in a complex multiple injection regimen. Biphasic lispro (Humalog Mix25/Mix50®) and biphasic aspart (NovoMix 30®) are now available in the UK (the number is the percentage of the soluble rapid-acting component of the mix). Mixtures of rapid-acting and protamine insulin have facilitated mealtime glycaemic control with faster insulin peaks and shorter periods of raised insulin concentrations than mixtures of short-acting and protamine insulin.

Monomeric insulins are now preferred in the ever more sophisticated pump devices for continuous subcutaneous insulin infusion (CSII). Use of these devices is increasing, and studies continue to affirm their success for selected patients.[16]

Future methods of insulin delivery

With increased use of insulin, and greater preference for intensive administration schedules, there is much interest in the prospect of needle-free injections and other methods of painless delivery. For individuals who remain uncomfortable with the very fine needles currently available, several needle-free delivery systems can be purchased in the UK, such as the Vitajet and the mhi-500. These devices produce a fine stream of insulin under high pressure to the skin. They can readily deliver small amounts of insulin, but usage so far has been limited. Other approaches to transdermal delivery by iontophoresis and microporation remain in research development.

Inhaled insulin

The large surface area of the lungs (more than 100 m^2) with its thin and highly vascularised epithelium provides an attractive site for rapid insulin absorption. Several aerosol devices have been developed for inhalation of insulin either as a dry powder or in solution (table 3) and clinical trials are on-going.[17-19] These are mainly focused on delivery of relatively small amounts of short-acting and rapid-acting insulins for mealtime 'top-up'. The main basal insulin dose in the trials is taken by conventional injection. Absorption via the pulmonary route is similar to or faster than subcutaneous injection of rapid-acting insulin, and the effect is

Key messages

- The need for tighter glycaemic control has encouraged greater use of intensive insulin therapy in patients with diabetes mellitus
- Long-acting insulin analogues, e.g. glargine (recently introduced) and detemir (awaiting regulatory approval), facilitate a flatter and more consistent 'basal' insulin supply
- Rapid-acting insulin analogues, e.g. lispro and aspart, provide mealtime insulin 'top-ups' to reduce post-prandial glucose excursions

longer lasting. Variability of absorption within an individual is small, but substantially affected by intercurrent respiratory conditions; and smoking increases bioavailability. Bioavailability is generally low, however, typically 5–10% of an injection. Thus, pulmonary insulin will be an expensive option. Important issues such as long-term effects on the structure and function of lung tissues are awaited.

Two examples of insulin inhaler devices that use different technologies are the Inhale system (Exubera®) by Pfizer and Aventis, and the Aradigm® system (AERx) by NovoNordisk. Exubera uses a fine powder formulation of particles ~5 μm in diameter, which penetrate deep into the lungs with slow inhalation. Aradigm uses a liquid aerosol with finer particles of ~2–3 μm. Good delivery is ensured by this device, as it releases insulin only when optimum flow rate and volume are achieved.

Oral insulins

Many attempts to produce an oral insulin formulation have been reported over the last three decades, including liposome-encapsulated insulin and various polymer-wrapped insulins. None has provided both an adequate shield against proteolytic digestion and an effective aid to absorption to give reasonable bioavailability. A recent promising contribution is an alkyl-polyethyleneglycol conjugated hexyl-insulin (HIM2) in clinical trial with Nobex and GSK. Others include a particulate 'nanocubicle' emulsion[20] and a polylactide microcapsule.[21]

Buccal and nasal insulins

Buccal insulin delivery is under clinical development by Generex and Lilly under the names of Oralin® in Europe and Oralgen® in the USA. Administration is similar to an angina spray, with an aerosol (RapidMist®) delivering a fine spray directly onto the buccal mucosa.

Nasal epithelium provides a very low bioavailability of insulin and is sensitive to intercurrent local infections and irritation. Surfactants and other absorption enhancers increase bioavailability, but have not led to a viable delivery system due to disturbances to the integrity of the nasal epithelium.[16]

Liver-targeted insulins

Subcutaneous injections of insulin do not replicate the normal physiological delivery of insulin into the portal circulation so that the liver is exposed to higher insulin concentrations than the periphery. Preferential delivery to the liver is under investigation using insulin linked to thyroxine (thyroxyl-insulin). This is highly protein bound and cannot therefore cross the endothelium, which prevents access to peripheral tissues. However, the liver has open sinusoids which allow free access to the hepatocytes.[22]

Masked insulin

Insulin has been linked to an organic complex that can be selectively broken by the catalytic aldolase antibody 38C2. The organic complex inactivates the insulin, but administration of the antibody can then be used to provide controlled release of active insulin.[23]

Conclusion

The advent of long-acting insulin analogues, to mimic basal insulin supply, and rapid-acting monomeric analogues, to emulate the post-prandial insulin response, should help patients achieve a more physiological daily glycaemic profile.

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Advances in insulin therapy: a commentary

It is now 80 years since the first therapeutic administration of insulin. Over the past 20 years insulin, with an amino acid sequence identical to that of human insulin, has become available. Recently, synthesised insulin analogues with different amino acid sequences to human insulin have been developed. They have revolutionised insulin therapy with their improved pharmacokinetics that closely mimic physiological endogenous insulin secretion.

There is a bewildering array of different types of insulin available, including animal and human types in monophasic and biphasic formulations, with variable onsets and durations of action. The choice is further complicated by the variety of insulin delivery devices, ranging from needles and syringes to pen devices and pumps that deliver a continuous subcutaneous infusion of insulin. A non-diabetes specialist might ask why we need so many. In this edition of the journal Day and colleagues[1] (see pages 379–83) have largely answered the question through their account of recent advances in insulin formulations and delivery methods. Importantly for the patient, the enhanced insulin pharmacokinetics of the recent analogues compared to standard human insulin formulations are associated with improved choice, convenience and flexibility. These can only translate into better compliance with therapy and improved quality of life, although this has not brought about vastly improved glycaemic control compared to standard insulin, as measured by glycosylated haemoglobin (HbA_{1C}). Nevertheless, increased availability of different insulin types does permit a tailored approach to therapy for most individuals with diabetes mellitus.

Insulin therapy in primary care

Insulin glargine is the first long-acting insulin analogue introduced into clinical practice in the UK. Its use is currently advocated for patients who are unable to achieve glycaemic control targets because of recurrent episodes of symptomatic hypoglycaemia associated with intensive insulin therapy, and for those who require assistance from a carer or a healthcare professional to administer insulin.[2] Initial feedback from patients and clinical audits indicate an advantage of glargine over conventional intermediate- and long-acting insulin, with a documented reduction in the perception of hypoglycaemia and improvement in treatment satisfaction.[3]

With the publication of the National Service Framework (NSF) for diabetes, and the introduction of the quality framework within the new GP contract, there is a growing pressure to initiate insulin therapy in the primary care setting. At present, few practices feel confident or have the resources to do so without recourse to specialist care or support, although the number willing to supervise insulin therapy is increasing. The administration of insulin is not a simple routine mechanical activity: it is a dynamic learning process involving an expert with adequate knowledge of the pharmacophysiology of insulin to be able to respond appropriately to changes in the patient's status, and a patient with sufficient understanding of the basis of insulin therapy, the necessary dietary adjustments, and the need for frequent blood glucose monitoring. This learning process should take place within a framework of continued support and education for both patient and expert.

To provide an ambulatory insulin commencement service within the community, possibly by practice nurses supported by diabetes specialist nurses, many issues need to be considered. These include the provision of protected time, adequate human resources and financial funding, specialist and ongoing training for staff, proper supervision, and open channels of prompt communication with secondary care. The establishment of consensus guidelines for insulin conversion and an agreement between hospitals and primary care trusts concerning the best use of diabetes specialist nurses are urgently needed, be it in hospital or community premises. Nurse-led prescribing and the resultant clinical governance issues pertaining to legal and accountability matters require clarification and appropriate statutory legislation.

Tailored insulin therapy

Individual tailored insulin therapy is paramount. The insulin regimen (type, dosage and frequency) must be individualised according to glycaemic response.

- In type 1 diabetics an intensive 'basal-bolus regimen' is often used. This comprises injections of rapid- or short-acting insulin before meals and (basal) intermediate-acting insulin, or more recently glargine, usually at bedtime.
- This intensive therapy is probably unnecessary for most patients with type 2 diabetes who require insulin. The appropriate total daily dose of insulin depends on the patient's concurrent oral glucose-lowering therapies, residual insulin secretory capacity, and degree of insulin resistance. Due to the insulin resistance of type 2 diabetes, large insulin doses (usually 0.5–1.0 units/kg body weight) are frequently required to achieve improved glycaemia. In combination with a glucose-lowering drug, a single dose of human Insulatard®, Monotard® or recently insulin glargine is usually started at 0.1 to 0.2 units/kg, either before breakfast or at bedtime. The insulin dose is increased by 2–4 units every 3–4 days to achieve a desirable fasting glucose.[4] If the daily insulin dose exceeds 30 units, the dose is usually split and one of several regimens is considered. These regimens include: two doses of intermediate-acting insulin, with (typically) two-thirds of the total daily requirement injected before breakfast and one-third before dinner; two daily injections using a 30/70 mixture of short- and intermediate-acting insulin; or a basal-bolus regimen.

All patients need to be reassured about the rationale for insulin and the process of its initiation. Important issues should be addressed, including patients' negative attitudes to insulin and misconceptions, which may be considered as the 'psychological insulin resistance syndrome'. These obstacles include: fear that insulin initiation signifies a worsening of their diabetes; aversion to needles and fear of the associated social stigma; perception of inconvenience, restrictions imposed by insulin therapy and difficulty in its administration; fear of hypoglycaemia and weight gain.

New insulin analogues are advantageous in addressing many of these fears, as well as simplifying the practicalities of insulin initiation. Notably, there is no longer a need to inject 20–30 minutes before a meal and the basal component of insulin glargine can be taken at any time of day. Thus, the time spent on education is expected to be shorter. Additionally, as discussed by Day and colleagues there may be successful non-injectable insulin preparations such as inhaled insulin in the future, which will mean that insulin and needles need not be synonymous in the minds of many patients.

Cardiovascular risk

The patient and his professional carer can also be reassured that there is no substantive evidence that exogenous insulin is directly linked to any risk of increased atherosclerosis or cardiovascular mortality. By contrast, prospective studies in non-diabetic subjects have suggested that it is the measured endogenous hyperinsulinaemia that is associated with increased cardiovascular mortality.[5] These adverse associations may be the result of the insulin resistance and other features of the metabolic syndrome rather than insulin *per se*. In the United Kingdom Prospective Diabetes Study (UKPDS), a key outcome trial in an exclusively diabetic cohort, there was no increase in cardiovascular events or mortality with exogenous insulin therapy compared to the conventionally-treated group.[6] There is evidence that insulin therapy in patients with acute myocardial infarction[7] and patients in intensive care units[8] is linked to reduced mortality. Although at present there are no immediate clinical safety concerns for insulin analogues, long-term observations in human subjects remain invaluable.

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Br J Cardiol 2003;**10**:383–4

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