REVIEW ARTICLE

Drugs 2005; 65 (3): 325-340
0012-6667/05/0003-0325/$39.95/0

A Critical Appraisal of the Role of Insulin Analogues in the Management of Diabetes Mellitus

Ralph Oiknine, *Marla Bernbaum* and *Arshag D. Mooradian*

Division of Endocrinology, Department of Internal Medicine, Diabetes, and Metabolism, St Louis University School of Medicine, St Louis, Missouri, USA

Contents

Abstract

Insulin is one of the oldest and best studied treatments for diabetes mellitus. Despite many improvements in the management of diabetes, the nonphysiological time-action profiles of conventional insulins remain a significant obstacle. However, the advent of recombinant DNA technology made it possible to overcome these limitations in the time-action profiles of conventional insulins. Used as prandial (e.g. insulin lispro or insulin aspart) and basal (e.g. insulin glargine) insulin, the analogues simulate physiological insulin profiles more closely than the older conventional insulins. If rapid-acting insulin analogues are used in the hospital, healthcare providers will need a new mind-set. Any error in coordination between timing of rapid-acting insulin administration and meal ingestion may result in hypoglycaemia. However, guidelines regarding in-hospital use of insulin analogues are few. The safety profile of insulin analogues is still not completely established in long-term clinical studies. Several studies have shown conflicting results with respect to the tumourigenic potential of this new class of agents. The

clinical implications of these findings are not clear. Although novel insulin analogues are promising 'designer drugs' in our armamentarium to overcome some of the limitations of conventional insulin therapy, cost may be a limiting factor for some patients.

The DCCT (Diabetes Control and Complications Trial),[1] as well as the UKPDS (United Kingdom Prospective Diabetes Study)[2] have demonstrated unequivocally that tight blood glucose control delays the onset and slows the progression of microvascular complications in both type 1 and type 2 diabetic patients, respectively. Recently, attention has also been focused on the benefits of treating hyperglycaemia with insulin in hospitalised patients with or without diabetes mellitus.[3-5] These studies have prompted a second look at defining the glycaemic targets for patients admitted to the hospital.[6]

Although some studies have suggested that insulin may be a risk factor for vascular disease,[7] the UKPDS showed that intensive insulin therapy was not associated with cardiovascular toxicity.[2] In fact, recent studies have shown that intensive insulin treatment reduces mortality in diabetic patients presenting with acute myocardial infarction.[4]

Insulin is one of the oldest and best studied therapeutic agents for the management of diabetes. All patients with type 1 diabetes and many patients with advanced type 2 diabetes require treatment with insulin. However, conventional insulin preparations cannot mimic the normal physiological insulin secretion. Despite many improvements in the management of diabetes using a multidisciplinary approach, the nonphysiological time-action profiles of currently available insulins remain an important obstacle towards achieving glycaemic goals. The newer insulin analogues have potential pharmacokinetic advantages. Over 300 insulin analogues have been studied, but only a few are currently available commercially. These include two rapid-acting insulin analogues, insulin lispro (Humalog®, Eli Lilly & Co., Indianapolis, IN, USA)[1] and insulin aspart (NovoLog®, Novo Nordisk Pharmaceuticals, Princeton, NJ, USA), along with their pre-mixed preparations, and one basal insulin analogue, namely insulin glargine (Lantus®, Aventis Pharmaceuticals, Bridgewater, NJ, USA). Insulin glulisine (Apidra™, Aventis Pharmaceuticals, Bridgewater, NJ, USA) and insulin detemir (Levemir®, Novo Nordisk Pharmaceuticals, Princeton, NJ, USA) are other insulin preparations that may soon be available in the US.

There are several excellent reviews of the role of insulin analogues in the management of diabetes.[8-16] In this update, we review the current and soon to be available insulin analogues, and discuss the advantages as well as potential concerns related to their widespread use.

1. Physiology of Insulin Secretion

In healthy nondiabetic patients, physiological insulin secretion by pancreatic β cells follows a pattern of basal and meal-stimulated insulin release. Basal insulin is secreted throughout the day and night at an approximate rate of 0.5–1.0 U/h.[17] The rate may vary depending on many confounding variables, such as exercise and changes in hormones that alter glucose metabolism. The main function of basal insulin secretion is to regulate basal hepatic glucose homeostasis in the fasting state and between meals or snacks. Postprandial insulin is released in a transient 2- to 5-minute burst (first phase) followed by a slow but progressive increase in insulin secretion for 5–52 minutes (second phase).[17] Insulin concentrations return to basal levels within 2–4 hours of a meal.[17]

In diabetic individuals, abnormalities in insulin secretion are at the core of the pathophysiology of the disease. While autoimmune destruction of pancreatic β cells renders almost all patients with type 1

1 The use of trade names is for product identification purposes only and does not imply endorsement.

diabetes completely dependent on exogenous insulin, patients with type 2 diabetes lose insulin secretory capacity more gradually and require insulin eventually as the disease progresses. It has been estimated that type 2 diabetic patients have a 40–50% reduction of β-cell function at the time of diagnosis and further decline continues over time.[18] In the early stages, insulin secretion increases in order to overcome insulin resistance. However, as the disease progresses, β-cell failure becomes more manifest. Not only does the quantity of insulin diminish with disease progression, but the timing of meal-stimulated insulin release is delayed, further compromising glucose homeostasis.[17] At the present time, it is not entirely clear whether this failure is secondary to 'exhaustion' of pancreatic β cells as they try to compensate for insulin resistance, or is the result of an inherent defect in islet cells of subjects prone to type 2 diabetes.[19,20]

In practice, when glycaemic goals are not met with diet, exercise and a combination of oral agents, insulin therapy must be introduced.[21,22] Many patients with type 2 diabetes are candidates for insulin therapy at the outset of the disease. These include those with severe hyperglycaemia (blood glucose >300 mg/dL), those who have allergy or intolerance to oral anti-diabetic agents, or during acute illness (such as systemic infection, myocardial infarction, surgery, renal and/or hepatic disease, and pregnancy). In many instances, insulin therapy requirements can be temporary.

2. Conventional Insulin Preparations

The goal in insulin replacement therapy in patients with either type 1 or type 2 diabetes is to mimic as closely as possible physiological insulin secretion. However, the pharmacodynamic profiles of conventional insulins, including short-acting regular insulin, intermediate-acting insulins (insulin lente [insulin zinc suspension] or insulin suspension isophane [NPH insulin]) and longer-acting insulin (insulin ultralente [extended insulin zinc suspension]), are suboptimal (table I). Following subcutaneous injection of soluble insulin, the hexameric zinc-containing insulin molecule, undergoes a series of dissociations and dissolutions. The resulting monomeric molecules are then capable of being absorbed through the capillary bed surrounding subcutaneous tissue. However, this rate-limiting step is not the only factor delaying insulin absorption. The site, depth, volume and concentration of insulin injected, along with the presence of factors affecting local blood flow to the area injected, such as smoking and temperature, can all delay or accelerate insulin absorption. Even under controlled conditions, insulin absorption is not consistent. Following insulin injection, intra-individual coefficient of variation with regard to peak insulin concentration, time to peak and area under the concentration-time curve, as observed during glucose clamp studies, can be as high as 50%.[23,24]

Short-acting regular insulin reaches its peak insulin action 2–3 hours following subcutaneous injection in the abdomen at a dose of 0.1–0.2 units/kg and can last up to 8 hours.[23,24] Injecting a larger dose, at a different site such as the thigh can further prolong time to peak action and duration. To bypass this slow absorption rate and avoid postprandial hyperglycaemia, regular human insulin is injected 30–60 minutes before a meal. However, this approach may be inconvenient for most patients, resulting in lack of compliance with proper timing of injection and inadequate postprandial glucose control. Furthermore, as the insulin concentration falls slowly after peaking, its extended duration of action may lead to inbetween meal and early morning hypoglycaemia.

Intermediate-acting insulins, insulin lente and insulin suspension isophane, have a delayed onset of action ranging between 2 and 4 hours, can take approximately 6–7 hours to reach peak concentration and can last up to 20 hours. This leads to a distinct peak and trough effect, causing wide variations in blood glucose. Therefore, when used as basal insulin, often two or more injections a day are required to minimise the daily excursions of insulin levels.

Long-acting insulin ultralente also poses similar problems. Its wide variability in onset (6–10 hours), peak action (10–16 hours) and duration (18–24

Table I. Some of the most commonly used insulin preparations (reproduced from Chehade and Mooradian,[25] with permission. © 2001 John Wiley & Sons)

Insulin (or insulin analogue) preparations	Action profile (h)			Constituents
	onset	peak	duration	
Ultra-rapid acting				
Insulin lispro	0.2–0.5	0.5–2	3–4	Similar to human regular insulin with transposed lysine and proline in the β-chain
Insulin aspart	0.2–0.5	0.5–2	3–5	Similar to human insulin with proline replaced by aspartic acid at B28
Short acting				
Regular insulin (human)	0.5–1	2–3	6–8	Solution of unmodified zinc insulin crystals
U-500 insulin (human)[a]	1–3	6–12	12–18	Concentrated unmodified
Intermediate acting				
Insulin suspension isophane (NPH) [human]	1.5	4–10	16–24	Protamine zinc, phosphate buffer
Insulin lente (insulin zinc suspension) [human]	1.5–3	7–15	16–24	Amorphous, acetate buffer
Insulin ultralente (human)	3–4	9–15	22–28	Amorphous and crystalline mix
Long acting				
Insulin glargine	3–4	No peak	20–30	An analogue of human insulin which crystalises in neutral solutions
Mixtures (human)[b]				
70/30	0.5–1	3–12	16–24	Insulin suspension isophane 70%, regular 30%
50/50	0.5–1	2–12	16–24	Insulin suspension isophane 50%, regular 50%
Mixtures (insulin analogues)				
75/25	0.2–0.5	0.5–2	16–24	Insulin neutral protamine lispro (NPL) 75%, lispro 25%
70/30	0.2–0.5	0.5–2	16–24	Neutral protamine aspart 70%, aspart 30%

a All other preparations available in the US are concentrated as U-100 (100 units/mL).

b Mixtures with different proportions of insulin suspension isophane and regular are also available in Europe.

hours) make it a less predictable preparation for use as basal insulin.[24]

3. Insulin Analogues

The advent of recombinant DNA technology made it possible to overcome the limitations in the time-action profile of conventional insulins. Used as prandial, meal-related bolus or as basal insulin, the analogues simulate physiological insulin profiles more closely than the older conventional insulins.

3.1 Rapid-Acting Insulin Analogues

Currently, there are three rapid-acting insulin analogues with very similar pharmacokinetic profiles. These include insulin lispro, insulin aspart and insulin glulisine. These analogues are present either in monomeric form or in very weakly bound hexameric form. They are rapidly absorbed in <30 minutes following subcutaneous injection and have a short time to peak insulin concentration of 1 hour and a shorter duration of action of 3–4 hours when compared with regular human insulin.[26-28] Furthermore, the intra-individual variability in time to maximum serum insulin concentration is significantly less for rapid-acting insulin analogues than for conventional insulin preparations.[26-28]

3.1.1 Insulin Lispro

Insulin lispro differs from human insulin by the substitution of proline with lysine at position 28 and lysine with proline at position 29 of the insulin β-chain (figure 1).[26] These substitutions result in a diminished tendency of the insulin molecule to self-associate. The change of the two amino acids in positions 28 and 29 was deduced from the structure

of insulin-like growth factor (IGF)-1, which, unlike insulin, does not tightly aggregate as hexamers. This may explain the higher affinity of insulin lispro, relative to human insulin, for the IGF-1 receptor reported in some studies.[29]

This 'ultra fast-acting' insulin is conveniently injected 5–15 minutes before a meal or immediately after a meal, resulting in better postprandial glucose control and less frequent late hypoglycaemia.[30] This is especially important for individuals who have dinner at late hours of the evening or before bedtime, as the prolonged action of regular insulin may influence the overnight period resulting in early morning hypoglycaemia. In children or older adults with dementia who have unpredictable eating patterns, rapid-acting insulin analogues may also offer potential benefits.[22] In these situations, the rapid-acting insulin analogues can be administered after the meal without excessive deterioration of glycaemic control.[31,32]

3.1.2 Insulin Aspart

Insulin aspart was designed with the single replacement of the amino acid proline by aspartic acid at position 28 of the insulin β-chain (figure 1).[27] Recent head-to-head trials have shown that the pharmacokinetic and pharmacodynamic profiles of insulin lispro and insulin aspart were identical in adult patients with type 1 diabetes.[33] However, other studies have found minor differences in the pharmacokinetics of these two rapid-acting insulin analogues.[34]

Insulin aspart was also shown to be as effective when administered pre-prandially and postprandially in a study in children and adolescents with type 1 diabetes.[35] This study found that glycaemic control was not worse with postprandial insulin injection as assessed by fructosamine and glycosylated haemoglobin (HbA_{1c}) values. To our knowledge, a similar study has not been performed in adult diabetic patients. This information could prove valuable in the treatment of diabetic patients with gastroparesis where insulin is often administered after meals as these patients often have difficulty in retaining the ingested food. Thus, delaying insulin administration post meal will ensure that the meal is completely retained and insulin dose is appropriate for the amount of carbohydrates consumed.

3.1.3 Insulin Glulisine

Insulin glulisine is a novel rapid-acting human insulin analogue produced by recombinant DNA technology, expected to be released in Europe and the US by mid 2005 (figure 1).[28] It is designed with the substitution of the amino acid lysine with asparagine at position 3 of the insulin β-chain and by substitution of the amino acid glutamine at position 29 by lysine. Preliminary euglycaemic clamp stud-

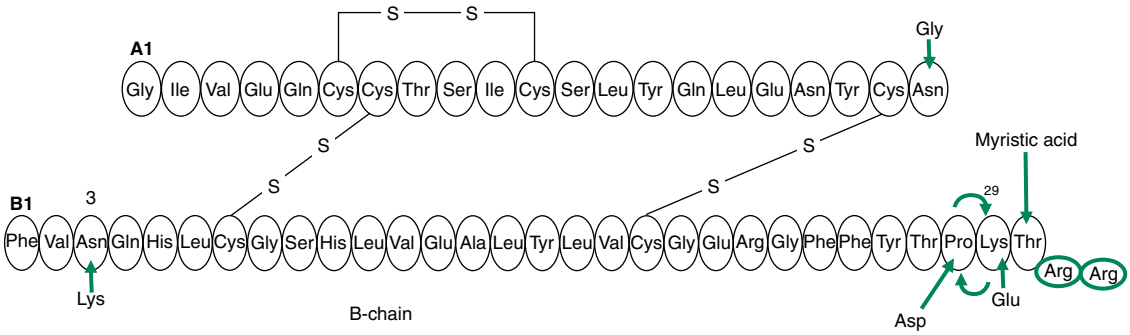

Fig. 1. The structural modifications of insulin found in some insulin analogues. Insulin lispro differs from human insulin by the substitution of proline with lysine at position 28 and lysine with proline at position 29 of the insulin β-chain; insulin aspart is designed with the single replacement of the amino acid proline by aspartic acid at position 28 of the human insulin β-chain; insulin glulisine is designed with the substitution of the amino acid lysine with asparagine at position 3 of the human insulin β-chain and by substitution of the amino acid lysine at position 29 with glutamine; insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the β-chain; insulin detemir is designed to bind albumin in plasma after absorption, threonine is omitted from position 30 of the insulin β-chain and replaced by myristic acid, a C14 fatty acid chain.

ies in animals and humans demonstrated that insulin glulisine is a rapid-acting insulin analogue with comparable pharmacodynamic and pharmacokinetic properties to insulin lispro.[36,37] Insulin glulisine has the unique property of predominantly activating the insulin receptor substrate-2 signaling pathway, which plays a crucial role in pancreatic β-cell growth and survival.[38,39] However, further studies are needed to characterise the true advantage of insulin glulisine over insulin lispro or insulin aspart.

3.1.4 Clinical Utility of Rapid-Acting Insulin Analogues

Although the overall glycaemic control may or may not differ with the use of rapid-acting insulin analogues compared with regular insulin,[40-42] their convenient administration allows more flexibility to both adults and children who eat unplanned meals or snacks. The ultra fast-acting insulin analogues are especially effective in attenuating postprandial blood glucose excursions in both type 1 and type 2 diabetic patients.[40-43] The clinical significance of postprandial hyperglycaemia and its link to increased cardiovascular disease and death in adult patients with diabetes has been previously described.[44,45] Whether rapid-acting insulin analogues decrease the incidence of cardiovascular disease and mortality in diabetic patients with postprandial hyperglycaemia remains to be determined.

Rapid-acting insulin analogues are not approved in pregnancy, although retrospective reviews of medical records of diabetic women treated with insulin lispro, before conception and throughout pregnancy, found that insulin lispro resulted in adequate glycaemic control, without adverse maternal or fetal outcomes.[46] Similar studies are underway with other insulin analogues, including the long-acting insulin glargine. The safety and efficacy of insulin analogues during pregnancy was recently reviewed.[47] A small short-term study evaluated the efficacy of insulin aspart in comparison with regular human insulin in women with gestational diabetes during standardised meal tests.[48] On three consecutive days, breakfast meal tests were performed; the first with no exogenous insulin and the other two after the injection of either regular insulin or insulin aspart. Effective postprandial glycemic control in these women was brought about by insulin aspart.[48] However, there are no prospective, randomised studies demonstrating the safety and efficacy of insulin analogues in pregnancy. Such studies are difficult and costly to conduct.

Buffered regular insulin was the only insulin approved for pump therapy until December 2001 when the US FDA issued approval for insulin aspart. Currently, insulin aspart and insulin lispro are approved for continuous subcutaneous insulin infusion (CSII) in type 1 and type 2 diabetic patients. In addition, a recent study also found that insulin glulisin is a well tolerated and effective alternative for insulin pump therapy.[49] Insulin aspart has been shown to be heat stable in pumps at 37ºC (98.6ºF) for up to 48 hours. The incidence of crystal formation and clogging in the pump reservoir and distal tubing is low.[50] A potential disadvantage of using rapid-acting analogues in insulin pumps is that pump malfunction and interruption of insulin delivery in type 1 diabetic patients will cause ketoacidosis faster than when regular insulin is used in the pump.[51]

Rapid-acting insulin analogues are also conveniently available in a syringe alternative form, namely the 'insulin pen'. The pen is pre-filled with an insulin cartridge and allows more flexibility for ambulatory patients. Once in use, it can be used for up to 14 days without refrigeration. Humalog® pen and NovoLog® FlexPen® come with a pre-filled 3-mL (300-unit) insulin cartridge. These insulin pens may be useful for patients with mild visual impairment and poor dexterity.

Local and systemic allergic reactions may occur following insulin analogue use. Although rapid-acting insulin analogues were thought to be less antigenic,[52] cases of allergy to insulin lispro and insulin aspart have been reported.[53] These case reports suggest that rapid-acting insulin analogues are not necessarily good alternatives to conventional regular insulin in this context.

3.2 Premixed Insulins and Insulin Analogues

Rapid-acting insulin analogues are also available in premixed preparations with rapid and intermediate insulin activity (table I). Free mixing of insulin may be difficult for some patients and may result in errors in accuracy. Fixed-premixed combinations may simplify the insulin regimen and reduce the number of daily injections.

Premixed conventional insulins Humulin® (Eli Lilly & Co., Indianapolis, IN, USA) and Novolin® (Novo Nordisk Pharmaceuticals, Princeton, NJ, USA) [70/30] consist of 70% insulin suspension isophane and 30% regular insulin. Humulin® (50/50) consists of 50% insulin suspension isophane and 50% regular insulin. In some countries additional premixed insulins with different proportions of insulin suspension isophane and regular insulin are also available.

Two types of premixed insulin analogues are available: Humalog® mix (75/25), a 75% insulin neutral protamine lispro (NPL) with 25% insulin lispro, and NovoLog® mix (70/30), a 70% insulin protamine aspart suspension with 30% insulin aspart.

Humulin® (70/30), Humalog® mix (75/25) and NovoLog® mix (70/30) are also available in a pen form. Each prefilled, disposable pen contains 300 units of insulin (as opposed to 1000 units in a vial of U-100 insulin) and is sold in a box containing five pens. It is important to note that the premixed pen, in use, should be stored at temperatures <30ºC (<86ºF) for no more than 14 days. Premixed insulins should not be mixed with other insulins.

When insulin lispro and the intermediate-acting insulin NPL are mixed, the time-action profile of each individual type of insulin is maintained.[54] In a 6-month randomised, open-label study, twice-daily administration of Humalog® mix (75/25) was compared with twice-daily administration of Humulin® (70/30) in 89 patients with type 2 diabetes.[55] Humalog® mix improved postprandial glycaemic control after morning and evening meals but did not improve the overall HbA_{1c} value.[55] This suggests that premixed insulin can be used for convenience in patients with already stable glycaemic control and that the rapid-acting insulin analogue component improves postprandial hyperglycaemia.

3.3 Basal Insulin Analogues

The conventional intermediate- and long-acting insulins including insulin suspension isophane, insulin lente and insulin ultralente do not simulate basal secretion of insulin. A reasonable alternative for both type 1 and type 2 diabetic patients on two daily injections of intermediate insulin, with or without rapid-acting insulin, or oral agents is the use of basal insulin analogues.

Insulin glargine and insulin detemir (soon to be available) are long-acting basal insulin analogues produced by recombinant DNA technology that have improved intra-individual variability.[16,24,56-59]

3.3.1 Insulin Glargine

Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the β-chain (figure 1).[58,59] Insulin glargine has a pH of approximately 4.0 and is a clear, completely soluble solution at that pH. Following subcutaneous injection, the acidic glargine solution is neutralised and forms microprecipitates. These microprecipitates slowly dissociate to hexamers, dimers and finally monomers capable of being absorbed across the capillaries. This process is slow but predictable.[16,59] Although it is a clear liquid, insulin glargine must not be diluted and cannot be mixed in the same syringe with other insulins as this would alter the pharmacokinetics of both insulins.

Insulin glargine has an onset of action of approximately 2 hours. It is relatively 'flat' and peakless compared with conventional intermediate- and long-acting insulins.[16,59] Small amounts of insulin glargine are absorbed and slowly released into the circulation, reaching a plateau of biological action at 4–6 hours and lasting up to 24 hours.

When compared with bedtime insulin suspension isophane in type 2 diabetic patients, insulin glargine was associated with less nocturnal hypoglycaemia (12.6% insulin glargine vs 28.8% insulin suspension isophane, $p = 0.011$).[60] Similarly, the Treat-to-Tar-

get Trial[61] showed that the addition of bedtime basal insulin glargine in type 2 diabetic patients, poorly controlled on one or two oral antidiabetic agents, was as safe and effective as bedtime insulin suspension isophane without causing nocturnal hypoglycaemia. However, nocturnal hypoglycaemia can occur, especially when insulin glargine is prescribed at bedtime. In practice, when nocturnal hypoglycaemia occurs, the timing of insulin glargine injection is changed to a morning injection. This is consistent with the findings of a recent study in patients with type 1 diabetes where insulin glargine was shown to be equally effective if administered before breakfast, before dinner or at bedtime, and nocturnal hypoglycaemia occurred in significantly fewer patients in the breakfast group.[62] In general, the timing of insulin glargine administration, therefore, is of minimal importance as long as it is administered at the same time every day.

Recent studies have suggested that use of insulin glargine along with a rapid-acting insulin supplement may result in glycaemic control comparable with that achieved with CSII. In an open-label parallel group study of 48 type 1 diabetic patients the efficacy of CSII and multiple daily insulin injection (MDI) treatment with insulin lispro plus insulin glargine were comparable.[63] However, in the CSII group there was a significantly greater reduction in mean amplitude of glycaemic excursions and insulin requirement than in the insulin glargine group. Despite a similar improvement in metabolic control, CSII improves blood glucose variability when compared with MDI with insulin glargine as basal insulin.[63] A similar conclusion was reached in a retrospective chart review of 150 patients with type 1 diabetes.[64]

3.3.2 Insulin Detemir

Insulin detemir is soluble basal insulin analogue at neutral pH with a unique mechanism of action. Insulin detemir is not yet available in the US, and there is very limited clinical experience with this type of insulin. It is designed to bind albumin in plasma after absorption. Threonine is omitted from position 30 of the insulin β-chain and replaced by myristic acid, a C14 fatty acid chain (figure 1).[57,65-67]

Following subcutaneous injection, insulin detemir binds to albumin via the fatty acid chain. At steady state, the concentration of free, unbound insulin is then greatly reduced, resulting in stable plasma glucose.[57,65-67]

The duration of action of insulin detemir is approximately 20 hours, as determined by isoglycaemic clamp studies, with a waning effect noted after 10–12 hours.[66] Therefore, insulin detemir is administered twice daily in most patients. As with other insulin analogues, insulin detemir has a stable, less variable pharmacokinetic profile than insulin suspension isophane or insulin ultralente.[67-70] Insulin detemir was recently compared with insulin suspension isophane in type 1 diabetic patients on a basal-bolus regimen using pre-meal, rapid-acting insulin aspart.[69] The risk of hypoglycaemia was found to be significantly reduced with insulin detemir. In addition, preliminary evidence suggests that weight gain commonly associated with insulin therapy may be avoided when insulin detemir is used.[71] It is not clear if the latter favourable effect is the result of decreased risk of hypoglycaemia or is secondary to a selective appetite-modulating effect of insulin detemir. These observations highlight a potential advantage of using insulin detemir rather than insulin suspension isophane, when twice-daily dosage is necessary.

3.3.3 Clinical Utility of Long-Acting Insulin Analogues

Once-daily administration of insulin glargine has potential benefits, especially for insulin-dependent and/or insulin-requiring diabetic patients with erratic schedules or lifestyles. For instance, patients on shift schedules, especially nightshifts, and travellers to different time zones can appreciate the convenience of a once-daily dosage insulin regimen and achieve improved glycaemic control.

Although insulin glargine can last up to 24 hours, a waning effect can be seen as early as 15 hours.[16] This may account for the fact that some patients require two doses of insulin glargine in a 24-hour period. However, there is no evidence that this regi-

men has any advantage over conventional twice-daily insulin suspension isophane administration and, as such, should be discouraged.

The insulin peaks and troughs seen following a single injection of insulin suspension isophane will be attenuated with the use of MDIs (figure 2). The degree of this attenuation depends on the frequency of insulin administration.[72] However, to achieve a near-peakless sustained insulin level, MDIs may be necessary and the timing of those injections must be consistent from day to day. The latter makes this approach less practical. The newer long-acting insulin analogues provide a more practical alternative. However, these analogues may also have some limitations. For instance, when the long-acting insulin analogues are administered once daily, there is the potential that there may be a gap in the background insulin coverage if the duration of action in a particular individual is <24 hours (figure 3a). Alternatively, if the duration of insulin action exceeds 24 hours, or the insulin analogue is given more frequently than its effective duration of action, then 'stacking' of insulin will occur and may cause hypoglycaemia (figure 3b). In such cases the administration time of the insulin is adjusted to assure that the 'stacking' occurs at times of the day when insulin requirements are higher.

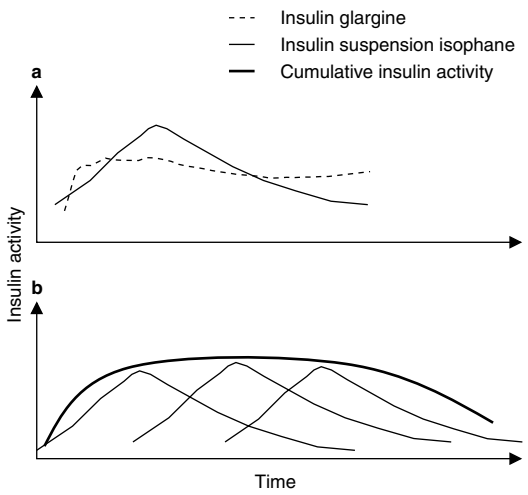

Fig. 2. Theoretical time-action profile of insulin glargine and insulin suspension isophane (**a**) after a single dose and (**b**) after repeated doses of insulin suspension isophane. The cumulative insulin activity in plasma and attenuation of peaks and troughs in serum levels of insulin seen following repeated doses of insulin suspension isophane is illustrated in (**b**). Insulin activity and time are shown in arbitrary units.

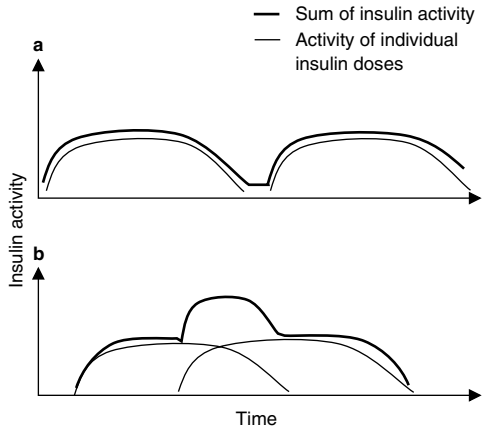

Fig. 3. Theoretical time-action profile of insulin glargine (**a**) when the duration of activity is shorter than the interval between injections and (**b**) when the duration of activity exceeds the interval between the injections. The potential for 'stacking' of insulin action is shown in (**b**). Insulin activity and time are shown in arbitrary units.

Although used by some clinicians, there are no safety or efficacy data available yet regarding the use of long-acting insulin analogues in special circumstances such as in pregnancy. There are limited data about the use of insulin glargine in end-stage renal disease and long-term haemodialysis. Insulin glargine was found to be effective in a small study of 20 diabetic patients with end-stage renal disease on long-term haemodialysis, as demonstrated by a decrease in HbA_{1c} from 7.7% to 6.8%, and was well tolerated, with no occurrence of hypoglycaemia.[73] Given the extended duration of insulin action in renal failure and the lack of predictable pharmacokinetics of insulin glargine in these patients, the actual dosage of insulin glargine needs to be carefully individualised to avoid hypoglycaemia.

Practical precautions for physicians and patients relate to the length of time a vial of insulin glargine can be safely used. Ambient temperature and exposure to light are important determinants of insulin shelf life. Open vials of insulin glargine should be discarded after 28 days, regardless of refrigeration. On the other hand, an unopened vial can maintain stability to the expiration date stated on the packag-

ing if refrigerated, but should not be frozen.[74] Nonadherence to these precautions may result in loss of potency and unexplained inconsistency in glycaemic control. It is noteworthy that the recommended duration of using insulin products varies with the type of insulin, and whether it is in a vial or pre-filled syringes or cartridges.[75] The recommendations for products available in the US are sometimes different from the recommendations for the same products available in Europe.[75] The reason for this apparent discrepancy in the American and European recommendations is not clear. Patients should consult with the pharmacists for determining the recommended duration of use of any insulin once a vial is started.

Another important clinical consideration is that the similar clear appearance of insulin glargine solution and the rapid- and short-acting insulins may cause errors in administering the correct insulin prescription. Patients using both kinds of insulin should be cautioned to take extra care, and to note the elongated shape of the insulin glargine vial compared with the other insulin types. Finally, one of the less appreciated errors in insulin administration is that inadvertent injection of insulin glargine intravenously will cause acute hypoglycaemia similar to regular or any short-acting soluble insulins. These potential clinical errors, especially the occasional confusion between the clear solution of insulin glargine and rapid-acting insulins, will be reduced with the use of insulin pens.

A simple approach has been proposed for transferring patients from insulin suspension isophane to insulin glargine. Patients receiving one daily dose of insulin suspension isophane can be initiated on an equivalent dose of insulin glargine. For patients taking two daily doses of insulin suspension isophane, the total daily units of insulin suspension isophane should be reduced by 20% and administered as one injection of insulin glargine, given at the same time each day. Adjustment of the dose is based on the fasting blood glucose. The insulin glargine dose can be increased by two units for every 20 mg/dL of fasting blood glucose over 100 mg/dL.[61] The dose should be adjusted no sooner than 3 days after the initial injection. Determining the correct dosage may require at least 5–7 days, depending on the patient. Three daily pre-prandial insulin injections are administered with supplemental rapid-acting insulin as needed until the correct dosage of insulin glargine is achieved. Many type 2 diabetic patients may require only one daily injection of insulin glargine without additional pre-prandial insulin.

Local or systemic allergy may occur with insulin glargine.[76] Thus, insulin glargine can not necessarily be used as an alternative to conventional intermediate- or long-acting insulin in the context of insulin allergy.

To date, there are limited clinical data for the use of insulin detemir. Theoretically, insulin detemir, given its neutral pH, can be mixed with other insulins. This property represents a potential advantage over insulin glargine that cannot be mixed with other insulins. However, at the present time it appears that this theoretical advantage will not be an option in clinical practice until pharmacodynamic and pharmacokinetic studies are performed to show that the pharmacokinetics of insulin action are not significantly altered following mixing. Additional clinical trials are needed to define the true clinical utility and limitations of this insulin analogue. Although the time-action profile of insulin detemir is similar to insulin suspension isophane in so far as having a peak, its predictable pharmacokinetics, decreased intra-subject variability and possibly reduced risks of hypoglycaemia and weight gain, make this insulin analogue an important novel tool in the management of diabetes.[77]

4. Insulin Analogues and Potential Mitogenicity

Although insulin analogues have more physiological pharmacokinetic and pharmacodynamic profiles, their safety profile is still not completely established. Several studies have shown conflicting results with respect to the tumourigenic potential of this new class of agents. Studies involving the insulin analogue Asp B10 revealed that a single amino acid substitution was associated with an increased

tumourigenic potential in Sprague-Dawley female rats.[78] In cultured human skeletal muscle cells, insulin glargine was found to be metabolically equivalent to human insulin, without mitogenic effects.[79] In a study using different cell lines, all four commercially available insulin analogues, as well as Asp B10, were compared with respect to insulin and IGF-1 receptor binding properties and metabolic and mitogenic potencies.[29] Using the human osteosarcoma cell line, insulin lispro showed a 1.5-fold increase in IGF-1 receptor binding, while insulin aspart resembled human insulin in its IGF-1 receptor binding affinity. The two long-acting basal insulin analogues revealed much different properties. Insulin glargine was found to have a 6.5-fold increased IGF-1 receptor affinity compared with human insulin, and was slightly more potent than insulin Asp B10. In contrast, insulin detemir was >5-fold less potent than human insulin in binding to the IGF-1 receptor and the insulin receptor.[29] Preliminary studies have found insulin glulisine to have mitogenic potential identical to regular human insulin.[38]

The implications of these findings are not clear. Although insulin glargine did not display augmented mitogenic effect in human skeletal muscle cell lines, mitogenic potencies, in general, correlate with increased IGF-1 receptor affinities. The *in vivo* ramification of this finding is not yet defined in terms of clinical safety. Furthermore, at supra-physiological insulin concentrations, often required in insulin resistant diabetic patients, the increased growth stimulating potential of insulin glargine is not known. Although suggested in several studies, the increased affinity for the IGF-1 receptors in other organs, such as the eye or the kidney, could potentially lead to the development of retinopathy, nephropathy and tumour promotion.[80,81] However, it is unlikely that the increased relative binding affinity of some insulin analogues to IGF-1 receptors would have significant clinical consequences given the fact that the contribution of the exogenous insulin to overall endogenous IGF-1 activity is modest and generally within the physiological daily variation in serum IGF-1 levels.

Toxicological studies have found that there was no difference in the incidence of mammary tumours reported in both mice and rats when comparing the insulin glargine groups with the sodium chloride, vehicle-control or insulin suspension isophane groups. There was increased subcutaneous malignant fibrous histiocytomas found at the injection site. This rodent specific effect was not dose dependent and was attributed to chronic tissue irritation and inflammation.[82] In these studies, there were no neoplastic findings to indicate that insulin glargine had a systemic carcinogenic potential in mice or rats. Similar studies in rodents could not demonstrate any evidence of embryotoxicity.[83] However, insulin glargine is currently not approved for use in pregnant women.

5. In-Hospital Use of Insulin Analogues

There is a growing body of evidence showing that in-hospital hyperglycaemia, in patients with and without pre-existing diabetes, is associated with deleterious consequences. Blood glucose reduction with insulin therapy improves the overall clinical outcome.[3-6] However, there is very little information about in-hospital use of insulin analogues.

Insulin utilisation protocols depend on the patient location, the resources available within each service or floor, and the anticipated procedures that the patient will undergo. In general, for those patients undergoing major surgery, especially cardiac surgery, and those admitted to the intensive care units, the most appropriate management would be the initiation of intravenous insulin drip with frequent monitoring and titration of dose. The intravenous insulin drip should utilise human regular insulin only, as there is no advantage in this setting of any currently available insulin analogues. For those patients who require less intensive care, or are transferred to general medical or surgical floors where nursing staff is not trained or willing to use insulin drip protocols, a subcutaneous insulin therapy would be implemented.

If rapid-acting insulin analogues are used in the hospital, most physicians and nurses will need a new mind-set. These insulin analogues should be admin-

istered 5–15 minutes prior to meals and the nursing staff should be appropriately trained to inject rapid-acting analogues when meal trays are at the bedside. Any error in coordination between timing of insulin administration and meal ingestion is likely to result in hypoglycaemia, given the fast-acting nature of rapid-acting analogues. Procedures, tests and doctors' visits cannot interrupt or delay a meal once rapid-acting analogues are injected. In addition, given the short duration of action, patients with type 1 diabetes who are advised to have nothing by mouth cannot be treated with the newer short-acting insulin analogues given every 6 hours unless they are on adequate basal insulin.

For preoperative inpatient management of type 1 diabetic patients on insulin glargine before hospitalisation, it is recommended that two-thirds of the usual bedtime glargine dose is given, and that intravenous 5% dextrose in water at 100 mL/h is started the night before surgery. All other insulins should be withheld on the morning of surgery.[6] For patients normally taking insulin glargine in the morning, the recommendation is to administer half the usual dose on the morning of surgery along with intravenous 5% dextrose in water at 100 mL/h.[6] Blood glucose exceeding 200 mg/dL should be controlled with small doses of short- or rapid-acting insulin. It is noteworthy that these recommendations are based on expert opinion rather than on reliable clinical trials. As such, it is imperative that blood glucose levels are monitored frequently during the perioperative period and that adjustments are made in the supplemental insulin dose or the rate of dextrose infusion to maintain target blood glucose values.

For type 1 diabetic patients managed with an intravenous insulin drip, either perioperatively or because of an inability to eat, intravenous glucose and insulin should continue until meals are resumed and fully tolerated. When switching from intravenous to subcutaneous insulin, the intravenous infusion should continue at least 2–3 hours following administration of subcutaneous insulin glargine. Supplemental rapid-acting insulin, such as insulin lispro or insulin aspart, should be administered 10–15 minutes pre-prandially regardless of the timing of injection of insulin glargine.

For patients with type 1 diabetes on insulin analogues at the time of hospitalisation who are able to eat, a simple approach may be to resume the home insulin regimen of basal and prandial insulin with adjustments in both basal and pre-meal insulin for additional requirements as a result of stress, corticosteroid administration and dietary changes. For patients on insulin suspension isophane before hospitalisation, the most practical approach is to continue the home insulin regimen and adjust the dose as needed with supplemental insulin. If the patient is discharged from the hospital, then home self blood glucose monitoring is required and patients should receive special instructions for supplemental insulin to control hyperglycaemia.[84]

Type 2 diabetic patients on insulin glargine who are admitted for an early morning procedure should be instructed to have their usual dose of insulin glargine at bedtime and to withhold all rapid- or short-acting insulins on the morning of the procedure. Intravenous 5% dextrose in water at 100 mL/h should be started the morning of the procedure, and short-acting insulin may be given for blood glucose >180 mg/dL at 4- to 6-hour intervals prior, during and after the procedure. When food intake is resumed and tolerated, the home insulin regimen may be started. If it is anticipated that the patient will not be able to eat for >24 hours, one-half or two-thirds of the insulin glargine dosage may be administered the evening of admission along with intravenous 5% dextrose in water at 100 mL/h. Capillary blood is monitored for glycaemic excursions every 4–6 hours.

6. Future Directions in Insulin Therapy

Since the discovery of insulin in the 1920s, considerable efforts have been made to improve insulin production, purification and pharmaceutical formulations. Insulin analogues with near-physiological pharmacokinetics and pharmacodynamics represent a substantial advance in the development of injectable insulin.

However, much of the current research revolves around the development of noninvasive methods of insulin delivery. Oral and inhaled insulin are at the forefront and have been the focus of attention, while other non-invasive routes of insulin administration such as the transdermal, sublingual, intranasal and rectal routes have so far met very little success, despite the use of absorption enhancers.[85]

The major limitation in the formulation of oral insulin is gastric enzymatic degradation resulting in poor gastrointestinal absorption of the insulin molecule. Modified insulin molecules use steric interference to resist enzymatic attacks. The use of conjugate technology results in chemical stability and prolongation of drug activity. However, pegylated oligomers interfere with binding at receptor sites resulting in low insulin bioavailability.[86] In a small study, escalating doses of the oral insulin product hexyl-insulin in 16 fasting insulin-deprived adult patients with type 1 diabetes have shown a dose-dependent decrease in blood glucose.[87]

Oralin™ (oral insulin spray) developed by Generex Biotechnology Corporation, Toronto, ON, Canada is a liquid aerosol insulin formulation (RapidMist™) encapsulated by absorption enhancers and delivered into the patient's mouth via a metered dose inhaler. However, the bioavailability of Oralin™ is low, its absorption unreliable and long-term safety data are very limited.[86]

The intrapulmonary route is an attractive non-invasive route of insulin administration as it offers a large surface area of drug delivery. However, certain factors are known to influence the efficiency of aserosolised insulin. Asthma, interstitial lung disease, smoking and exercise can all interfere with proper deposition of aserosolised insulin particles into the alveoli and circulation, thereby reducing the bioavailability of the drug.[88]

Current clinical experience with inhaled insulin is mainly derived from two types of inhaled insulin formulations and delivery devices. The 'Inhale' delivery system (Inhale Therapeutic Systems, Palo Alto, CA, USA) uses a dry powder insulin formulation, and AERx® insulin Diabetes Management System (Aradigm Corporation, Hayward, CA, USA) uses a liquid aerosol insulin formulation. Preliminary studies have found inhaled insulin pharmacokinetics to be as rapid as insulin lispro but have duration of action that is more similar to regular insulin.[88-90]

Long-term efficacy and safety data with inhaled insulin are limited. The potential clinical effects of insulin-binding antibodies on the pharmacokinetics of inhaled insulin, and the clinical significance of a decrease in lung diffusion capacity associated with inhaled insulin therapy in some individuals, calls for further investigation.[91]

7. Conclusion

It can be argued that the first insulin analogues utilised clinically were those extracted from bovine and porcine pancreatic tissues. The advent of recombinant human insulin was heralded as an important achievement as it abrogated the need to rely on animal sources and was associated with significantly reduced immunological responses to insulin therapy. However, the pharmacokinetic limitations of the animal and human insulin, especially in the fast- or short-acting forms, prompted further research into developing insulin analogues with more favourable pharmacokinetic profiles.

Recent studies have shown that flexible intensive insulin management can be cost effective and the advent of insulin analogues has enhanced flexibility and convenience for insulin-treated patients.[92] The increased flexibility in insulin timing is also associated with an improvement in quality-of-life measures. Use of insulin aspart was associated with significantly greater improvement in treatment satisfaction than human regular insulin in one study.[92] Improved satisfaction was mainly due to increased dietary and leisure time flexibility. Similarly, quality-of-life studies show consistently increased treatment satisfaction with insulin lispro compared with human regular insulin. Finally, several studies have found that treatment with insulin lispro is cost effective in terms of reducing episodes of severe hypoglycemia and reduced hospitalisation when compared with human regular insulin.[93]

The ideal basal/bolus insulin combination, which exactly reproduces the 24-hour physiological insulin secretory pattern, is not yet available. Novel insulin analogues are promising 'designer drugs' in our armamentarium to overcome some of the limitations of conventional insulin therapy. Achieving the American Diabetes Association recommended goal of an HbA_{1c} of 7% is now more feasible, provided that the fundamentals of diabetes management, including home self blood glucose monitoring, carbohydrate counting, diet and exercise, are consistently applied.

However, these new insulins are more expensive than conventional insulins and this may be a limiting factor for some patients. For patients without insurance coverage the price of older insulin products is less than half the price of insulin analogues, and that is not even considering the higher prices when pen devices are used. In addition, it is prudent to remember that the long-term safety of insulin analogues is not known.[94] For safety purposes, long-term follow-up of large numbers of patients using insulin analogues should be carried out. Furthermore, well designed studies should be performed in pregnant women to establish the safety profile of these agents for both the mother and the child.

Although structural modification of the insulin molecule has led to the development of insulins that have better time-action profiles and are more convenient to use, the cost remains an obstacle for wider use of insulin analogues in clinical practice.

Acknowledgements

The manuscript was partially supported by a fellowship training grant from Eli Lilly and Co.

References

1. DDCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 1993; 329: 977-86
2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-53
3. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001; 345: 1359-67
4. Malmberg K, for the DIGAMI (Diabetes Mellitus Insulin – Glucose infusion in Acute Myocardial Infarction) Study Group. Prospective randomized study of intensive insulin treatment on long-term survival after acute myocardial infarction in patients with diabetes mellitus. BMJ 1997; 314: 1512-5
5. Umpierrez GE, Isaacs SD, Bazargan N, et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002; 87: 978-82
6. Trence DL, Kelly JL, Hirsh IB. The rationale and management of hyperglycemia for in-patients with cardiovascular disease: time for change. J Clin Endocrinol Metab 2003; 88: 2430-7
7. Depres JP, Lamarche B, Mauriege P, et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 1996; 34: 952-8
8. Wang F, Carabino JM, Vergara CM. Insulin glargine: a systematic review of a long-acting insulin analogue. Clin Ther 2003; 25: 1541-77
9. Ristic S, Bates PC. Effects of rapid-acting insulin analogs on overall glycemic control in type 1 and type 2 diabetes mellitus. Diabetes Technol Ther 2003; 5: 57-66
10. Gerich JE. Novel insulins: expanding options in diabetes management. Am J Med 2002; 113: 308-16
11. Vajo Z, Duckworth WC. Advances in the treatment of diabetes-insulin analogues. Minerva Endocrinol 2002; 27: 167-80
12. Vajo Z, Fawcett J, Duckworth WC. Recombinant DNA technology in the treatment of diabetes: insulin analogs. Endocr Rev 2001; 22: 706-17
13. Dunn CJ, Plosker GL, Keating GM, et al. Insulin glargine: an updated review of its use in the management of diabetes mellitus. Drugs 2003; 63 (16): 1743-78
14. Gomez-Perez FJ, Hernandez-Jimenez S, Aguilar-Salinas CA, et al. Insulin analogues: a critical review. Rev Invest Clin 2002; 54: 527-41
15. Chapman TM, Noble S, Goa KL. Insulin aspart: a review of its use in the management of type 1 and 2 diabetes mellitus. Drugs 2002; 62 (13): 1945-81
16. McKeage K, Goa KL. Insulin glargine: a review of its therapeutic use as a long-acting agent for the management of type 1 and 2 diabetes mellitus. Drugs 2001; 61 (11): 1599-624
17. Cook DL, Taborsky Jr GJ. B-cell function and insulin secretion. In: Porte D, Sherwin RS, editors. Ellenberg and Rifkin's diabetes mellitus. 5th ed. Philadelphia (PA): Lippincott-Raven, 1997: 49-73
18. UK Prospective Diabetes Study 16. Overview of 6 years' therapy of type 2 diabetes: a progressive disease. UK prospective Diabetes Study Group. Diabetes 1995; 44: 1249-58
19. Gerich JE. Contributions of insulin-resistance and insulin-secretory defects to the pathogenesis of type 2 diabetes mellitus. Mayo Clin Proc 2003; 78: 447-56
20. Gerich JE. Is insulin resistance the principal cause of type 2 diabetes? Diabetes Obes Metab 1999; 1: 257-63
21. American Diabetes Association. Clinical practice recommendations 2004. Diabetes Care 2004; 27 Suppl. 1: S15-35
22. Chahade JM, Mooradian AD. A rational approach to drug therapy of type 2 diabetes mellitus. Drugs 2000; 60: 95-113
23. Heinemann L, Richter B. Clinical pharmacology of human insulin. Diabetes Care 1993; 16 Suppl. 3: 90-100
24. Lepore M, Pampanelli S, Fanelli C, et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analogue glargine, NPH insulin, ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes 2000; 49: 2142-8

25. Chehade JM, Mooradian AD. Drug therapy: current and emerging agents. In: Sinclair AJ, Finucane P, editors. Diabetes in old age. 2nd ed. Chichester: John Wiley & Sons, 2001: 199-214
26. Howey DC, Bowsher RR, Brunelle RL, et al. (Lys(B28), Pro(B29))-human insulin: a rapidly absorbed analogue of human insulin. Diabetes 1994; 43: 396-402
27. Simpson KL, Spencer CM. Insulin aspart. Drugs 1999; 57 (5): 759-65
28. Barlocco D. Insulin glulisine Aventis Pharma. Curr Opin Investig Drugs 2003; 4: 1240-4
29. Kurtzhals P, Schaffer L, Sorensen A, et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. Diabetes 2000; 49: 999-1005
30. Chase HP, Lockspeiser T, Peery B, et al. The impact of the Diabetes Control and Complications Trial and Humalog insulin on glycohemoglobin levels and severe hypoglycemia in type1 diabetes. Diabetes Care 2001; 24: 430-4
31. Rami B, Schober E. Postprandial glycaemia after regular and lispro insulin in children and adolescents with diabetes. Eur J Pediatr 1997; 156: 838-40
32. Rutledge KS, Chase HP, Klingensmith GJ, et al. Effectiveness of postprandial Humalog in toddlers with diabetes. Pediatrics 1997; 100: 968-72
33. Hedman CA, Lindston T, Arnqvist HJ. Direct comparison of insulin lispro and aspart shows small differences in plasma insulin profiles after subcutaneous injection in type 1 diabetes. Diabetes Care 2001; 24: 1120-1
34. Homko C, Deluzio A, Jimenez C, et al. Comparison of insulin aspart and lispro, pharmacokinetic and metabolic effect. Diabetes Care 2003; 26: 2027-31
35. Danne T, Aman J, Schober E, et al. A comparison of postprandial and preprandial administration of insulin aspart in children and adolescents with type 1 diabetes. Diabetes Care 2003; 26: 2359-64
36. Becker R, Frick A, Wessels D, et al. Pharmacodynamics and pharmacokinetics of a new, rapidly-acting insulin analog, insulin glulisine [abstract]. Diabetes 2003; 52 Suppl. 1: 471-P
37. Wermer U, Gerlach M, Hofmann M, et al. Insulin glulisine is a novel, parenteral, human insulin analog with a rapid-acting time-action profile: a crossover, euglycemic clamp study in normoglycemic dogs [abstract]. Diabetes 2003; 52 Suppl. 1: 590-P
38. Rakatzi I, Ramrath S, Ledwig D, et al. A novel insulin analog with unique properties, LysB3, GluB29 insulin induces prominent activation of insulin receptor substrate 2, but marginal phosphorylation of insulin receptor substrate 1. Diabetes 2003; 52: 2227-38
39. Rakatzi I, Seipke G, Eckel J. [LysB3, GluB29] insulin: a novel insulin analog with enhanced beta-cell protective action. Biochem Biophys Res Commun 2003; 310: 852-9
40. Home PD, Lindholm A, Hylleberg B, et al. Improved glycemic control with insulin aspart: a multicenter randomized double-blind crossover trial in type 1 diabetic patients. Diabetes Care 1998; 21: 1904-9
41. Anderson Jr JH, Brunelle RL, Keohane P, et al. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulin-dependent diabetes mellitus. Arch Intern Med 1997; 157: 1249-55
42. Anderson Jr JH, Brunelle RL, Koivisto VA, et al. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Diabetes 1997; 46: 265-70
43. Plank J, Wutte A, Brunner G, et al. A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. Diabetes Care 2002; 25: 2053-7
44. Gerich JE. Clinical significance, pathogenesis, and management of postprandial hyperglycemia. Arch Intern Med 2003; 163: 1306-16
45. Mooradian AD, Thurman JE. Drug therapy of post-prandial hyperglycemia. Drugs 1999; 57: 19-29
46. Garg SK, Frias J, Anil S, et al. Insulin lispro therapy in pregnancies complicated by type 1 diabetes: glycemic control and maternal and fetal outcomes. Endocr Pract 2003; 9: 187-93
47. Gamson K, Chia S, Jovanovic L. The safety and efficacy of insulin analogs in pregnancy. J Matern Fetal Neonatal Med 2004; 15: 26-34
48. Pettitt DJ, Ospina P, Kolaczynski JW, et al. Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. Diabetes Care 2003; 26: 183-6
49. Hanaire-Broutin H, Schumicki D-M, Hoogma RPLM, et al. Safety of insulin glulisine compared with insulin aspart administered by continuous subcutaneous insulin infusion (CSII) [abstract]. Diabetes 2004; 53 Suppl. 2: A4
50. Bode BW, Strange P. Efficacy, safety, and pump compatibility of insulin aspart used in continuous subcutaneous insulin infusion therapy in patients with type 1 diabetes. Diabetes Care 2001; 24: 68-72
51. Guerci B, Meyer L, Salle A, et al. Comparison of metabolic deterioration between insulin analog and regular insulin after a 5-hour interruption of a continuous subcutaneous insulin infusion in type 1 diabetic patients. J Clin Endocrinol Metab 1999; 84: 2673-8
52. Ottensen JL, Nilsson P, Jami J, et al. The potential immunogenicity of human insulin and insulin analogues evaluated in transgenic mouse model. Diabetologia 1994; 37: 1178-85
53. Takata H, Kumon Y, Osaki F, et al. The human insulin analogue Aspart is not the almighty solution for insulin allergy. Diabetes Care 2003; 26: 253-4
54. Heise T, Weyer C, Serwas A, et al. Time-action profiles of novel premixed preparations of insulin lispro and NPL insulin. Diabetes Care 1998; 21: 800-3
55. Roach P, Yue L, Arora V. Improved postprandial glycemic control during treatment with Humalog Mix25, a novel protamine-based insulin lispro formulation. Humalog Mix25 study group. Diabetes Care 1999; 22: 1258-61
56. Scholtz HE, Pretorius SG, Wessels DH, et al. An assessment of the variability in the pharmacodynamics of HOE 901 compared to NPH and ultralente human insulins using euglycemic clamp technique [abstract]. Clin Pharmacol Ther 2000; 67: 123
57. Heinemann L, Sinha K, Weyer C, et al. Time-action profile of the soluble, fatty acid acylated, long-acting insulin analogue NN304. Diabet Med 1999; 16: 332-8
58. Rosskamp RH, Park G. Long-acting insulin analogs. Diabetes Care 1999; 22 Suppl. 2: B109-13
59. Gerich JE. Insulin glargine: long-acting basal insulin analog for improved metabolic control. Curr Med Res Opin 2004; 20: 31-7
60. Yki-Jarvinen H, Dressler A, Ziemen M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. Diabetes Care 2000; 23: 1130-6
61. Riddle M, Rosenstock J, Gerich J. The Treat-to-Target Trial: randomized addition of glargine or human NPH insulin to oral

therapy of type 2 diabetic patients. Diabetes Care 2003; 26 (11): 3080-6

62. Hamann A, Matthaei S, Rosak C, et al. A randomized clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with type 1 diabetes. Diabetes Care 2003; 26: 1738-44
63. Lepore G, Dodesini AR, Nosari I, et al. Effect of continuous subcutaneous insulin infusion vs multiple daily insulin injection with glargine as basal insulin: an open parallel long-term study. Diabetes Nutr Metab 2004; 17: 84-9
64. Harmel AP, Mathur R. Similar A1C outcomes in type 1 diabetic patients undergoing intensive diabetes management with preprandial rapid-acting insulin and either CSII or glargine. Diabetes Care 2004; 27: 272-3
65. Markussen J, Havelund S, Kurtzhals P, et al. Soluble, fatty acid acylated insulins bind to albumin and show protracted action in pigs. Diabetologia 1996; 39: 281-8
66. Kurtzhals P, Haveland S, Jonassen I, et al. Albumin binding and time action of acylated insulins in various species. J Pharm Sci 1996; 85: 304-8
67. Pieber TR, Plank J, Goerzer E, et al. Duration of action, pharmacodynamic profile and between-subject variability of insulin detemir in subjects with type 1 diabetes [abstract]. Diabetes 2002; 51 Suppl. 2: A53
68. Danne T, Lupke K, Walte K, et al. Insulin detemir is characterized by a consistent pharmacokinetic profile across age-groups in children, adolescents, and adults with type 1 diabetes. Diabetes Care 2003; 26: 3087-92
69. Vague P, Selam JL, Skeie S, et al. Insulin Detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type1 diabetes on a basal-bolus regimen with premeal insulin Aspart. Diabetes Care 2003; 26: 590-6
70. Kurtzhals P. Engineering predictability and protraction in a basal insulin analogue: the pharmacology of insulin detemir. Int J Obes 2004; 28 Suppl. 2: S23-8
71. Fritsche A, Haring H. At last, a weight neutral insulin? Int J Obes 2004; 28 Suppl. 2: S41-6
72. Ross EM. Pharmacodynamics: mechanisms of drug action and the relationship between drug concentration and effect. In: Hardman JG, Gilman AG, Limbird LE, editors. Goodman and Gillman's: the pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill, 1996: 29-41
73. Pscherer S, Schreyer-Zell G, Gottsmann M. Experience with insulin glargine in patients with end-stage renal disease [abstract]. Diabetes 2002; 51 Suppl. 2: A53
74. Grajower MM, Fraser CG, Holcombe JH, et al. How long should insulin be used once a vial is started. Diabetes Care 2003; 26: 2665-9
75. Gallo M, Comoglio M, De Micheli A, et al. Insulin storage in Europe. Diabetes Care 2004; 27: 1225-6
76. Durand-Gonzalez KN, Guillausseau N, Pecquet C, et al. Glargine insulin is not an alternative in insulin allergy [letter]. Diabetes Care 2003; 26: 2216
77. Chapman TM, Perry CM. Insulin detemir: a review of its use in the management of type 1 and 2 diabetes mellitus. Drugs 2004; 64 (22): 2577-95
78. Schwartz GP, Burke T, Katsoyannis PG. A super active insulin: (B10-Aspartic acid) insulin (human). Proc Natl Acad Sci U S A 1987; 84: 6408-11
79. Ciaraldi TP, Carter L, Seipke G, et al. Effects of the long-acting insulin analog insulin glargine on cultured human skeletal muscle cells: comparisons to insulin and IGF-1. J Clin Endocrinol Metab 2001; 86: 5838-47
80. Blakesley VA, Stannard BS, Kalebic T, et al. The role of the IGF-1 receptor in mutagenesis and tumor promotion. J Endocrinol 1997; 152: 339-44
81. Grant MB, Names RN, Fitzgerald C, et al. Insulin-like growth factor I acts as an angiogenic agent in rabbit cornea and retina: comparative studies with basic fibroblast growth factor. Diabetologia 1993; 36: 282-91
82. Stammberger I, Bube A, Durchfeld-Meyer B, et al. Evaluation of the carcinogenic potential of insulin glargine (LANTUS) in rats and mice. Int J Toxicol 2002; 21: 171-9
83. Hofmann T, Horstmann G, Stammberger I. Evaluation of the reproductive toxicity and embryotoxicity of insulin glargine (LANTUS) in rats and rabbits. Int J Toxicol 2002; 21: 181-9
84. Glister BC, Vigersky RA. Perioperative management of type 1 diabetes mellitus. Endocrinol Metab Clin N Am 2003; 32: 411-36
85. Owens DR. New horizons: alternative routes for insulin therapy. Nat Rev Drug Discov 2002; 1: 529-40
86. Still JG. Development of oral insulin: progress and current status. Diabetes Metab Res Rev 2002; 18 Suppl. 1: S29-37
87. Clement S, Still JG, Kosutic G, et al. Oral insulin product Hexyl-Insulin Monoconjugate 2 (HIM2) in type 1 diabetes mellitus: the glucose stabilization effects of HIM2. Diabetes Technol Ther 2002; 4: 459-66
88. Laube BL. Treating diabetes with aerosolized insulin. Chest 2001; 120: 99-106
89. Cefalu WT. Inhaled human insulin treatment in patients with type2 diabetes mellitus. Ann Intern Med 2001; 134: 203-7
90. Skyler JS, Cefalu WT, Kourides IA, et al. Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomized proof of concept study. Lancet 2001; 357: 331-5
91. Quattrin T, Belanger A, Bohannon NJ, et al. Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneaous insulin therapy in patients with type 1 diabetes: resuilts of a 6-month, randomized, comparative trial. Exubera Phase III Study Group. Diabetes Care 2004; 27: 2622-7
92. Bott U, Ebrahim S, Hirschberger S, et al. Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in patients with type 1 diabetes. Diabet Med 2003; 20: 626-34
93. Dunn CJ, Plosker GL. Insulin lispro: a pharmacoeconomic review of its use in diabetes mellitus. Pharmacoeconomics 2002; 20: 989-1025
94. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database of Systematic Reviews 2004; (2): CD003287

Correspondence and offprints: Dr *Arshag D. Mooradian*, Division of Endocrinology, Saint Louis University Medical School, 1402 South Grand Blvd, St Louis, MO 63104, USA. E-mail: mooradad@slu.edu