Subcutaneous insulin: pharmacokinetic variability and glycemic variability

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SUMMARY
The therapeutic goal in insulin-treated diabetic patients is to maintain on the long-term a tight glucose control (HbA1c < 6.5-7% or less) through an insulin regimen which “mimic” the physiological insulin profile: a basal insulin secretion to maintain glucose homeostasis and an acute post-prandial secretion in response to meal intake. Such goal represents a challenge for the clinician as conventional human insulins have major drawbacks: slow absorption and too late peak with regular insulins, delayed peak and often occurring at an unwanted time with intermediate and long-acting insulins. Furthermore, these insulins are characterised by a large within- and between-subjects variability, which complicate patients’ task to self-adapt their daily doses, even for those well educated and compliant. These limitations and unpredictable variations in insulin action are responsible for an increased risk of hypoglycemic events, between meals as well as during the night period. As a consequence, glucose control is frequently insufficient in type 1 diabetic patients, and these limitations may contribute also to the delayed initiation of insulin therapy in type 2 diabetics when oral antidiabetic agents fail. This variability and the non-reproductibility of the conventional insulin pharmacodynamics are explained by several exogenous and endogenous factors described in this review. Availability of new short-acting (lispro, aspart and glulisine) and long-acting analogs (glargine, detemir) of human insulin, with improved pharmacokinetic characteristics, and a lesser variability and better reproducibility, should facilitate a tight glucose control in insulin-treated patients. The main pharmacokinetic and pharmacodynamic characteristics of these new insulin analogs are presented and discussed in the light of there intra- and interindividual variability. Their reduced variability should permit to reinforce near “physiological” insulin regimen such as “basal-bolus” technique and to consider new approaches and therapeutic strategies in type 1 and type 2 diabetic patients.

Key-words: Insulin analogs · Insulin pharmacodynamics · Insulin pharmacokinetics · Insulin therapy regimen · Insulin-treated diabetes · Glycemic control · Glycemic variability · Hypoglycemia.

Guerci B, Sauvanet JP. Subcutaneous insulin: pharmacokinetic variability and glycemic variability. Diabetes Metab 2005,31,4S7-4S24

RéSUMÉ
Insulinothérapie sous-cutanée : variabilité pharmacocinétique et variabilité glycémique
Chez le patient diabétique insulinotraité, l’objectif thérapeutique est de maintenir à long terme un strict contrôle glycémique (HbA1c < 6,5-7% ou moins), tout en se rapprochant du profil physiologique de la sécrétion d’insuline, c’est-à-dire une sécrétion basale suffisante pour maintenir l’homéostasie glycémique et une réponse postprandiale à la prise alimentaire. Ceci représente un véritable challenge pour le clinicien dans la mesure où les insulines humaines conventionnelles souffrent de plusieurs limites : une absorption lente et un pic tardif pour les insulines d’action rapide, un pic retardé mais souvent gênant pour les insulines d’action intermédiaire ou à longue durée d’action. De plus, ces insulines se caractérisent par une extrême variabilité intra et interindividuelle compliquant la tâche des patients pour l’adaptation des doses journalières, même ceux bien éduqués qui appliquent les consignes du personnel soignant. Ces limites et variations imprévisibles de l’action de ces insulines sont responsables d’un risque accru d’épisodes hypoglycémiques, tant entre les repas qu’en période nocturne. La conséquence en est souvent un contrôle glycémique insuffisant chez les patients diabétiques de type 1, et cela contribue également au recours généralement trop tardif à l’insulinothérapie chez les patients diabétiques de type 2 en échec des antidiabétiques oraux. Cette variabilité et la non-reproductibilité de l’action pharmacodynamique des insulines conventionnelles s’expliquent par de nombreux facteurs endogènes et exogènes décrits dans cet article. La mise à disposition d’analogues rapides (insulines lispro, aspart et glulisine) et d’analogues de longue durée d’action (insulines glargine et detémir) de l’insuline humaine, aux propriétés pharmacocinétiques améliorées, avec une moindre variabilité et une meilleure reproductibilité, devrait permettre d’atteindre plus facilement des objectifs glycémiques stricts chez les patients insulinotraités. Les principales caractéristiques pharmacocinétiques et pharmacoénergiques de ces nouveaux analogues de l’insuline humaine sont présentés et discutés selon le niveau de variabilité intra et interindividuel. Cette moindre variabilité devrait permettre de renforcer les schémas insuliniques « physiologiques » de type basal-bolus, mais également d’envisager de nouvelles approches et stratégies thérapeutiques, tant chez les patients diabétiques de type 1 que de type 2.

Mots-clés: Analogues de l’insuline · Contrôle glycémique · Diabète insulinoto-traité · Effets pharmacocinétiques de l’insuline · Hypoglycémie · Pharmacocinétique de l’insuline · Schéma insulinique · Variabilité glycémique.

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Diabetes Metab 2005,31,4S7-4S24 • © 2005 Masson, all rights reserved
Several long-term studies have provided conclusive evidence that maintaining tight glycemic control (HbA1c < 7%) can prevent the onset or delay the progression of microvascular complications in insulin-treated patients, either with type 1 or type 2 diabetes [1, 2]. In the DCCT (Diabetes Control and Complications Trial) study, intensified insulin treatment in type 1 diabetic patients reduced the incidence of late diabetic complications and delayed the progression of existing microvascular complications compared to conventional regimens [1, 3]. However, intensified insulin therapy was associated with a greater risk of hypoglycemia [4]. The incidence of severe hypoglycemic episodes in the intensive arm of the DCCT was about three times higher than in the conventional therapy arm, with severe episodes occurring in about 30% of patients [4, 5]. In the UKPDS (United Kingdom Prospective Diabetes Study), type 2 diabetic patients who achieved tight glycemic control, usually involving insulin therapy, had a reduced risk of progression of microvascular diseases but, as in the DCCT study, at the expense of a greater risk of hypoglycemia. In this study, symptomatic hypoglycemia was reported in 76% of type 2 patients assigned to insulin, with major hypoglycemic episodes requiring third-party assistance or hospitalization occurring in 11% of patients over 6 years [6]. Results from both the DCCT and the UKPDS studies demonstrated that there is no threshold value for HbA1c below which further risk reductions in diabetes-related complications cannot be achieved with improved control [3, 7]. Thus, until recently, conventional insulin regimens used to achieve tight glycemic control, reduce long-term diabetic complications but with the need of complex intensified regimens, potential risk (and danger) of hypoglycemia and patient’s inconvenience, and often fair of unexpected hypoglycemia.

The challenge for the clinician is to reach the recommended glycemic target (HbA1c < 7%, and preferably < 6.5%) and to maintain on the long-term a near-normoglycemia [8]. This has to be achieved through a more physiological insulin replacement, without increasing the demand on the patient and in minimising the risk of hypoglycemia or other adverse events (such as weight gain) related to tight insulin delivery.

In non-diabetic subjects, normal insulin secretion consists of two major components: a chronic low basal release and a meal related surges in secretion. The role of the low-level basal insulin secretion, critical to the maintenance of basal euglycemia, is to modulate the rate of overnight hepatic glucose production and glucose output between meals. This pancreatic insulin secretion in the basal state varies from 0.25 to 1.5 U/h and accounts for 50% or more of the 24-hour integrated insulin secretion and permit to maintain basal glucose levels within a narrow range [9, 10]. Rapid meal-related insulin secretion, controls and limits post-prandial blood glucose excursions of about 0.40 g/l which occur within 15 minutes following a meal and reach a peak 30-45 minutes later, the amount of secretion being tailored to the carbohydrate content of the meal [11]. Then, glucose levels return to basal levels (generally within 1 to 2 hours) and remained stable until the next meal, with insulin levels following the same pattern [9, 11, 12] as illustrated Figure 1. In non-diabetic individuals, these components and the reactivity of insulin secretion in response to various situations (food ingestion, composition and time of consumption, physical activity, etc.) ensure a physiological action of insulin and glucose homeostasis, permitting blood glucose stability and reproducibility from one day to another [13].

**“Physiologic” insulin replacement therapy: a challenge for the clinician!**

The 24-h plasma glucose and insulin physiological profiles in non-diabetic individuals according to meal size and time of day of meal ingestion. Plasma glucose (in grey); plasma insulin (in black). p = 0.02-0.001 heavy meal vs light meal and p = 0.006 18:00 a.m. vs 6:00 p.m. [adapted from ref. 11].
In diabetic patients, the aim of insulin therapy is to mimic normal (“physiological”) insulin patterns. Therefore, an ideal insulin replacement regimen should be able to accurately reproduce both the basal and prandial/post-prandial insulin secretion profile in order to achieve a complete near-normal 24-hour a day glycemic control. This is attempted through the “basal-bolus” insulin regimen, an attempt to reproduce both the basal and meal-induced components of normal insulin secretion. Unfortunately, until now, no combination of conventional insulin preparations was able to satisfactorily replicates normal insulin secretion patterns, and a considerable variability in the action of insulin is observed, jeopardizing physician’s and patient’s attempts to a better blood glucose control [14, 15]. This is mainly due to several factors, either exogenous or endogenous, but clearly, conventional subcutaneous insulin preparations have major limitations in their pharmacokinetic profile [16].

Several studies have demonstrated that continuous subcutaneous insulin infusion (“insulin pumps”) provides better glycemic control (assessed by HbA1c levels) and reduces the rate of hypoglycemia [17, 18]. These effects are largely due to a lower variability and a greater predictability in day-to-day absorption of insulin than with multiple daily insulin injections, resulting in a better blood glucose stability, as a result from a smaller subcutaneous insulin depot and the sole use of rapid-acting conventional human insulin or insulin analogs without the need for long-acting insulins [19-21]. This is particularly the case when diabetic patients are treated with an insulin analog in external pumps, as demonstrated in studies with the short-acting insulin analog lispro [22-24] as well as with the use of the high technology of programmable implantable insulin pump, as the route of intraperitoneal insulin delivery is more physiological in such case [25]. Unfortunately, these therapies, often looked as “a gold standard”, remain accessible to a limited number of insulin-treated patients only, although large variation are seen across countries (approximately 7,500 diabetic patients in France, mainly type 1 diabetics, but approximately 25,000 in Germany, 5-6% of them being type 2 insulin-treated diabetic patients) [2003 unpublished data presented at the symposium “Looking to the future: Innovative technologies for insulin delivery and glucose sensing”, Aix-en-Provence, August 30-31, 2003]

New insulin preparations, namely insulin analogs, may facilitate a more physiological (“basal-bolus”) regimen and contribute to achieve the physician’s challenge by permitting to the patients an optimised, more flexible and reproducible intensive self-management [26, 27].

Variability in insulin action: why? which factors?

The variability in insulin action is related to various factors, either linked to the insulin preparation or to the injection conditions, or to the organism itself, which may affect the diffusion of insulin or the interaction between insulin and its receptor. The variability, which represent the variation between patients (inter-individual variability) or for the same patient (intra-individual variability) of a given insulin preparation, is generally expressed as the coefficient of variation (CV) of the time required for 50% of the insulin to disappear from the injection site or as the CV in the pharmacodynamic action, depending of the method of assessment used (cf. § 3). It has also to be noted that generally, due to differences in tissue insulin sensitivity, pharmacodynamic parameters are more variable than pharmacokinetic parameters [28].

Pharmacokinetic variability of the conventional insulin formulation and its factors have been described in details in specific reviews [20, 29], and more recently by Gin and Hanaire-Broutin [16].

Factors linked to the insulin preparation

Physiologically, insulin is produced in pancreatic β-cells, where at high concentration in the presence of zinc ions, it self-associates into hexamers for efficient storage within vesicles. After exocytosis, dilution causes an immediate dissociation of insulin hexamers in dimers, then in biologically active monomers [30]. When defining a pharmaceutical insulin formulation, it has to be at a concentration in which insulin is hexomeric to be therapeutically useful, i.e. of an acceptable physical stability and of a tolerable subcutaneous injection volume. Following injection, the dilution of the insulin depot (predominantly constituted by insulin hexamers) is rather slow, as well as its dissociation into dimers and monomers. This means a slower diffusion through the tissue and a slower penetration within the capillary wall than physiological monomeric insulin. In addition, this low rate of entry into the systemic circulation means a greater dependence to local environmental factors such as blood flow rate [31]. Dissociation into monomers is the only way for insulin to diffuse into the interstitial fluid, to cross the blood barriers, and ultimately to bind to the insulin receptors located on the surface of the target organs. The delay to entry into the blood stream depends on physicochemical properties of the insulin formulation, and generally, more complex are the physicochemical characteristics, greater is the pharmacokinetic profile variability following a standardized injection, both between and within individuals [16, 29, 31].

In practice, this explains why a pre-prandial administration of a short-acting conventional insulin preparation results in a less than optimal blood glucose control. The rate of increase of portal and peripheral insulin concentration in the early phase of glucose absorption by the intestine are insufficient as the insulin peak is reached after only 90 to 150 minutes, and consequently blood glucose increases excessively 1 to 2 hours after meal ingestion. This explains the recommendations to inject insulin at least 30 or 45 minutes before the meal, to try to ensure that the maximal insulin concentration coincides with the post-meal hyperglycemic peak. But, 3 to 5 hours after the insulin injection, the continuing absorption from the subcutaneous depot results in an inappropriate
excess of circulating insulin levels with an increased risk of hypoglycemia by the time the meal absorption is nearly complete [26, 32].

- Short-acting (regular) conventional insulin are presented as a solution that form hexamers spontaneously. As described before, their action start 15 to 30 minutes after the subcutaneous injection, plasma concentrations reach a peak after 1-2 hours and decline slowly within 4 to 8 hours, although various values were reported depending on the different formulations and conditions of measurements. Under controlled experimental conditions in healthy volunteers, subcutaneous injection results in an intra-individual coefficient of variation (CV) of 10% in pharmacokinetic and of 15-25% in some pharmacodynamic parameters which characterize the metabolic effect of injected insulin. The inter-individual variability being generally 10% greater than the intra-individual variability.

- Intermediate- and long-acting, protamine or zinc-based, conventional insulins, are soluble insulin pharmaceutically designed for a slower rate of absorption, either by the addition of protamine (a protein from fish sperm) to a neutral solution of insulin, the neutral protamin Hagedorn (NPH) insulin, or by adding a suspension of zinc in excess to a neutral solution of soluble insulin (lente/ultralente insulin). Both formulations are presented in crystalline form and requires adequate shaking to destructure it and to release the insulin complexes which will self-aggregate as hexamers. Intermediate-acting insulin acts after 45-60 minutes with a peak in the pharmacokinetic profile and action 3 to 6 hours after injection, followed by a steady decline, with a pharmacodynamic effect for 8 to 10 hours. Long-acting insulin acts after 2 to 4 hours with a variable peak after 7 to 10 hours and their effect last for about 20 hours. Both of them exhibit wide variations in action between patients. Their subcutaneous absorption are commonly described as “extremely variable” and to present an even greater inter-individual variability (> 50%) than subcutaneous regular insulin [21, 29, 33]. They exhibit an intra-individual variability of around 20% in strict experimental conditions, although in a glucose clamp study, subcutaneous injection of NPH to healthy volunteers led to an intra-individual CV in the range of 12-45% [29]. In less controlled conditions, the intra-individual CV based on pharmacodynamic parameters is always greater: 20 to 40% for NPH and 38 to 55% for ultralente, and even greater in clinical practice [16]. For intermediate insulin, the combination of a peak in effect and the unpredictability of the time and extent of this peak inevitably incurs a greater risk of hypoglycemia, particularly at night as they are often dosed in the evening. The wide and unpredictable variation in the duration of action of long-acting insulin may result, when injected in the morning, either in an insufficient effect on glycaemia the following late part of the night (which may be conjugated with a “dawn phenomenon”) or in an increased risk of hypoglycemia by daytime when increasing the dose to increase plasma insulin availability at dawn [26].

Effects of insulin concentration and insulin dose

It is well demonstrated that the concentrations and doses of insulin play a role [16]. For a same insulin, the higher is the concentration, the slower is the diffusion. The absorption time is prolonged, which results in a longer duration of insulin effect. This may be the case also when dose is greater, as for instance, half-time for subcutaneous resorption of NPH is 7 hours for 8 units, but 12 hours for 25 units. However, increasing the dose not only reduces the rate of diffusion, but also results in an increase in the intra-individual CV, either with fast-acting human insulin or NPH insulin.

Factors linked to the injection conditions

Several factors linked to the injection conditions may affect the pharmacokinetic of insulin, resulting in a large day-to-day variability and poor reproducibility for a given patient. If the speed or injection doesn’t seem to affect the diffusion process, various other factors such as the site and depth of injection, delay before withdrawing the needle, etc., as well as blood flow in the subcutaneous tissue modifies the insulin resorption and diffusion and induce a large variability [16].

- Insulin temperature: although sometimes discussed, increase in insulin temperature may accelerate subcutaneous absorption.

- Injection site: Several pharmacokinetic studies have demonstrated the influence of the site of injection. Insulin diffuses faster when injected in the abdomen, more slowly when injected in the upper arm, and even slower when injected in the femoral region, insulin peak may occur up to 1 h later after injection into the thigh vs into the abdomen. Half-time for absorption of subcutaneous regular insulin was reported to be 3 h when injected in the thigh, 2.5 h in the arm and 1 h in the abdomen wall [20, 34, 35]. This variability in absorption according to the site of subcutaneous injection was nicely demonstrated by Koivisto et al. in seven insulin-treated diabetic patients, using 125I-labeled short-acting insulin [34] (Fig. 2). Obviously this causes wide differences in the duration of action. As an example, conventional regular insulin when injected in the abdomen starts its hypoglycemic effect after 20-40 min and its total duration of effect is 5-7 h vs 25-50 min and 6-8 h respectively when injected in the thigh [36]. These differences seems to be related to the different degree of vascularisation in the subcutaneous tissue, and perhaps also to insulin degradation in some tissue.

- Depth of the insulin injection: Deeper is the injection, more rapid is the diffusion [37]. This was clearly demonstrated in 11 insulin-dependent diabetic patients by intra-muscular injection of 125I-labeled NPH insulin with a twice faster absorption, a more rapid rate of insulin diffusion and consequently a shorter duration of action than when subcutaneously injected [33] (Fig. 3). In addition, the intra-individual CV is significantly higher when insulin is injected intra-muscularly than with subcutaneous injection (29.8% and 18.4% respectively, p < 0.01) as well as the inter-individual variabilities.
CV (50.0% and 18.4% respectively, p < 0.0001) [33]. In clinical practice, inadvertently intra-muscular injections are likely to be frequent, particularly in case of injection in the thigh or the arm when the length of the needle is not adapted to the subcutaneous tissue thickness. The risk to inject insulin into the muscle is particularly high in lean type 1 diabetic children, especially the boys, when using a 12.7-mm needle to inject insulin in the thigh or the arm [38]. This is due to a reduced thickness of adipose tissue with the muscular fascia close to the skin surface; this leads the authors to propose the use of short needles (8-mm length) and to use a two-finger pinch to ensure a cutaneous fold for each insulin injection to minimize this risk of intramuscular injection [38]. Needle position is also a frequent cause of accidentally intramuscular injection, particularly in lean diabetics with very thin subcutaneous tissue layer when using a vertical injection technique and 12-13 mm needle, this may be more frequent with pens and the recommendation to use them vertically as the respective

Figure 2
Effect of the subcutaneous injection site (thigh, arm or abdomen) on the variability of short-acting (regular) conventional insulin absorption in insulin-dependent diabetic patients, assessed by the disappearance time of 125I-insulin [adapted from ref. 34].

Figure 3
Effect of the depth of injection (guided by ultrasound) on the disappearance time of insulin after injection in the thigh of 10 IU of 125I-labeled NPH insulin, either intramuscularly (IM) or subcutaneously (SC) [adapted from ref. 33].
positions of the pen and of the injection site greatly influence the subcutaneous absorption [21, 39]. As a consequence, ADA (*American Diabetes Association*) recommendation indicates "thin individuals or children can use short needle or may need to pinch the skin and inject at a 45° angle to avoid intramuscular injection, especially in the thigh area" [40].

- **Time of residence of the needle during the injection (or time before withdrawing the needle):** Rapid withdrawal of the needle may induce an insulin reflux from the subcutaneous tissue (but also from the insulin pens), causing a variable loss of administered insulin. Although usually small, this insulin loss is frequent as demonstrated in studies where near 25% of the patients loose up to 18% of the dose administered with a syringe [41, 42]. This loss may be substantially greater with insulin pens in case of too rapid withdrawal, as in such case the insulin from the cartridge may not be fully injected and will continue to flow from the pen [42].

- **Subcutaneous blood flow:** Increase in blood flow, recruitment of capillaries or increase in the exchange surface will result in a shorter distance and time for the insulin to reach the blood stream. Conditions which will modify local blood flow, such as warm bath, physical exercise, use of vasodilating or vasoconstricting drugs, etc., will also modify insulin diffusion and increase insulin variability [16, 21].

- **Use of crystallised insulin (NPH, zinc):** Use of crystallised insulin requires vigorous shaking (~ 10 times for vials and ~ 20 times for pens) to create a suspension before injection. If not properly done, destructuration of the crystalline form is incomplete and insulin concentration is lower than planned. This translate in wide variations (near 100% or even more) in all pharmacokinetic and -dynamic parameters, including duration of insulin action. Inter-individual variability is generally reported to be ~ 50% and intra-individual variability ~ 25% [43, 44].

**Endogenous factors of variation**

These intrinsic factors may be due to progressive organ alterations, such as renal insufficiency, which alters insulin kinetics but doesn’t amplify the intra-individual day-to-day coefficient of variability [45] or to external phenomena (as intense physical activity) which may modify the absorption rate of subcutaneous insulin (intense exercise may cause a 50% increase in absorption rate [46]) and/or its glycemic effect. Age may be a factor too, a tendency towards a shorter duration of action for short-acting insulin was reported when comparing elderly (mean age 70.5 yrs) to middle-aged (mean age 53.7 yrs) type 2 diabetics with a comparable BMI (mean 30-31 kg/m²) [47], but this may be due to other confounding factors and requires further confirmation. Obesity, although discussed, may be a factor by delaying the delivery of insulin to interstitial fluid and then insulin action, due to a defect in insulin-mediated capillary recruitment [48].

However, the most significant factor is the hypo- and hyperglycemic effect. Both hypoglycemia and plasma glucose changes within the supraphysiologic range trigger the release of the glucose counterregulatory hormones with a transient insulin-resistance, consequently a defined dose of insulin injected immediately after a hypoglycemic episode will produce a smaller, non-modifiable, pharmacological effect than usually [32, 49, 50]. Among the glucose counterregulatory factors, increased glucagon secretion, which stimulates hepatic glycogenesis and favors hepatic gluconeogenesis, plays a primary role, as well as increased epinephrere secretion which stimulates hepatic glycogenesis, hepatic and renal gluconeogenesis, the latter largely by mobilizing gluconeogenic substrates. In non-diabetic subjects, glucagon and epinephrine act within a few minutes to raise plasma glucose. However, in type 1 diabetic patients, both insulin, glucagon and epinephrine secretion are impaired which cause a defective glucose counterregulation and a reduced rate of endogenous glucose production in response to hypoglycemia. The mechanism of the loss of glucagon response to the glucose concentration decrease is not fully known but is tightly linked to, and possibly the result of endogenous insulin deficiency [49, 51]. The role of the endogenous insulin deficiency was underlined in the DCCT where in the intensive treatment group, patients with high and sustained levels of stimulated C-peptide had a significantly reduced prevalence (~ 30% less, p < 0.05) of severe hypoglycemia than those with minimal or undetectable C-peptide [52]. This was confirmed by a study in selected type 2 diabetic patients with a long-standing requirement for insulin therapy (a clinical surrogate for endogenous insulin deficiency), in whom low plasma C-peptide concentrations (in the range usually found in type 1 diabetics) and a virtually absent glucagon response to hypoglycemia were documented, in contrast with the normal or moderately reduced response in most type 2 diabetic patients [49, 53]. The epinephrine response is attenuated and shifted towards lower glucose concentration, largely as a consequence of recent prior hypoglycemia [49, 54].

A particular clinical situation is the "brittle" diabetes, characterized by a predominant glycemic unstability with repeated ketoacidosis and/or severe hypoglycemics, leading to life disruption and recurrent and/or prolonged hospital admissions [55, 56]. Quantification of glycemic unstability and optimization of glucose control are particularly difficult in these patients. Although they represent a small number of diabetic patients (381 cases in a national survey conducted amongst all diabetologists in Great-Britain, i.e. a prevalence of 3/1,000 type 1 diabetic patients) [57], they need to be actively identified [57].

**Methods to assess insulin variability**

The variability in the insulin action can be measured by the pharmacokinetics of insulin (evolution of plasma insulin levels following injection, an indirect approach) and by the pharmacodynamic effects (the hypoglycemic action, which corresponds to the true insulin effect). Variability can be assessed and expressed in a number of ways, but two of the
most common measurements are standard deviation (SD) and coefficient of variation (CV). Both measures provide information on how tightly the individual characteristics are clustered around the mean, and in both cases, the bigger is the value, the greater is the variance. However, CV is more commonly reported as having the advantage over SD to be calculated from the mean and the SD of the sample to give a percentage, this facilitates comparisons between studies and insulin preparations [58].

Pharmacokinetic insulin measurements

– Radio-labelled insulins: The use of 125I-labelled insulins is limited to pharmacokinetic studies in healthy volunteers. The absorption of insulin from subcutaneous sites is usually assessed by the rate of disappearance of radioactivity after injection of the radio-labelled preparation. However, some controversy still exists as radio-labelled insulin may not behave identically to unlabelled one. They are degraded at the injection site and their irregular spreading in the hypodermic tissue layers may result in artefactually low absorption half-times [46]. Nevertheless, using this technique in healthy volunteers, Galloway et al. were able to demonstrate that following subcutaneous insulin injection of a single dose of 0.2 U/kg, the within-subject CVs for maximum insulin concentration and time to reach this peak were 44% and 68% respectively for NPH insulin and 28% and 34% respectively for lente insulin [59].

– Unlabeled insulin: Some studies have used unlabelled insulin but with difficulties in differentiating between administered and endogenous insulin when plasma concentrations are measured in healthy subjects, while in insulin-dependent diabetics, binding to circulating insulin antibodies (when present) may cause problems [46]. Another approach was used to establish the level of fluctuation of serum glargine concentrations in comparison to conventional insulins (ultralente and NPH). Mean serum levels of these insulins were analysed using an analytical method, and a complex fluctuation analysis tool was used, based on the geometric mean values over a 24-hour period (F24), expressed as F24 alone and F24 as a percentage of deviation around the average serum insulin concentration (PF24), lower values indicating a more physiological stable basal insulin profile [60].

Pharmacodynamic assessments

The methodology is generally based on clamp studies, either the well-known euglycemic glucose clamp (glucose level maintained within the normal range) or an isoglycemic clamp (i.e. plasma glucose target set at a slight hyperglycemic level of ~1.30 g/l to better approach the realistic clinical situation of intensive insulin therapy in type 1 diabetes). This latter technique being used by the group of Bolli [61]. Pharmacodynamic effect is assessed by the glucose infusion rate (GIR) necessary to maintain blood glucose levels constant, and recorded (ideally every minute) for 24-hour (or more) post-dosing. Then, the GIR profiles are statistically treated to allow for the determination of various pharmacodynamic endpoints (areas under the glucose infusion rate profiles in various intervals and/or post-meals, minimum plasma glucose concentration, time to reach minimum glucose concentration, etc.) as well as for the determination of the within- and between-subject variances or SD. In the study by Galloway et al. previously mentionned [59], injections of NPH and lente insulins were associated with marked variability in minimum plasma glucose concentration and time to reach minimum plasma glucose concentration; the within-subject CVs were 32% and 30% respectively for NPH and 21% and 34% respectively for lente insulins. However, choice of the endpoint may considerably influence the results and conclusions as illustrated in a pharmacodynamic study performed by Scholtz et al. aimed to compare the pharmacodynamic effect of insulin glargine vs NPH and ultralente insulins, results on intra-individual CV obtained from an euglycemic clamp were notably different when using the 12-h vs the 24-h AUC of glucose infusion [62].

The continuous glucose monitoring by different devices (CGMS®, GlucoDay® and others) might be an useful tool to study glucose variability. Specific tools of measurement or calculation can evaluate the intra-day glycemic variations or excursions (MAGE), the day-to-day glycemic variations or excursions on successive 24-h periods (MODD) which represents the true variability of insulin action from one day to another, area under the curve of glucose concentration, M coefficient, etc. [13, 63]. These parameters, currently used in clinical practice to optimize the therapeutic regimen in some patients, and their limits, were recently reviewed [64]. They may represent in the future an useful approach, particularly MODD to evaluate the intra-subject variability over a 24-h period. Currently, the new softwares of the glucose sensors can provide some of these indices of glucose variability, directly from the data collected throughout several consecutive days of recording.

Insulin analogs: an approach to reduce insulin variability

As indicated, limitations of conventional insulin make difficult for insulin-treated patients, even when properly educated and compliant, to maintain near-normoglycemia on the long-term. Slow and variable absorption of insulin from the subcutaneous site of injection and their day-to-day variability as well as the peak-action profile of these insulins, contribute to instability of blood glucose with wide fluctuations, somewhat unpredictable, from hypoglycemic values (particularly at night) to hyperglycemic values (notably at fast in the morning and post-meal). Thus, the pharmaceutical research to develop short-acting insulin analog absorbed faster and with less variability than regular human insulin and able to improve 1-h and 2-h post-prandial blood glucose levels, which together with a reproducible subcutaneous absorption, peak-
less long-lasting analog preparation that mimics the flat interprandial insulin secretion of non-diabetic subjects, will permit to approach the goal of a near-normoglycemia.

**Short-acting insulin analogs**

Two short (rapid)-acting analogs (lispro and aspart) are currently available, a third one (glulisine) was recently granted (June 2004) an European marketing approval. Substitutions or minimal alterations in the amino-acid sequence relative to human insulin result in insulin molecules with a reduced tendency to self-aggregate and a virtually instantaneous dissociation of the hexameric complex into monomeric subunits upon subcutaneous injection, increasing their absorption rate into the blood and resulting in a faster onset and a shorter duration of action. Rapid onset of action means they can be administered immediately before meal (within 5 minutes before it) with an improved convenience for the patient, additionally their shorter duration of action, and to some extent their reduced intra-individual variability, have the potential to reduce the risk of hypoglycemia [26, 32].

**Insulin lispro [review in 65-67]**

Insulin lispro (Lys$^\text{B28}$,Pro$^\text{B29}$ human insulin) is based on amino-acid substitution by reversing the natural sequence of proline at position B28 and lysine at position B29. This reversal leads to a conformational shift in the C-terminal end of the B chain that sterically hinders the ability of the insulin monomers to form dimers [65]. Pharmacokinetic studies demonstrated a significantly higher and earlier peak serum insulin concentration after subcutaneous injection than after regular conventional insulin. However, in contrast to regular conventional insulin whereas increasing doses result in an increase in the length of time to the peak activity of insulin, increasing the dose of insulin lispro does not result in changes in the length of time to the peak activity of insulin which appears independent of the dose [68], indicating a lower variability of the subcutaneous absorption with insulin lispro (Fig. 4). Pharmacodynamic studies have shown that the rate of glucose infusion needed to maintain euglycemia followed a similar pattern. This translates in a duration of action shorter (~ 3 h) than that of regular insulin, and in an intra-individual variability in the absorption of insulin lispro from subcutaneous injection sites somewhat less pronounced than regular human insulin. However, most of the factors which influence absorption of regular insulin, influence the absorption of insulin lispro also (site of injection, heat, etc.), even if their effects appear less pronounced than for regular human insulin [36, 65]. Increases in the injected dose of insulin lispro does not modify the time to the peak activity. However, carbohydrate and fat content of the meal, greatly influence the glucodynamic effect of insulin lispro [69, 70]. A decreased intra-individual variability in serum insulin concentrations and time to the peak of insulin lispro in healthy volunteers and in diabetic patients was reported as compared to regular human insulin (CV of 9.9% to 15.2% vs 23.8% to 24.4% respectively, depending of variables and conditions) without differences between the greater inter-individual CV of these insulins [67, 71].

![Figure 4](image-url)

**Figure 4**

Effect of increasing insulin dose on the length of time to the maximal peak activity and duration of action according to the various doses subcutaneously injected, comparison between the short-acting (rapid) insulin analog lispro and a regular conventional insulin in normal subjects [adapted from ref. 68].
Insulin aspart [review in 72-74]

Insulin aspart is identical to human insulin except aspartic acid substituted for proline at position B28. Pharmacokinetic and -dynamic studies in type 1 diabetics comparing insulin aspart to regular human insulin demonstrated a quicker absorption with a peak concentration within 30-70 minutes (vs 80 to 140 minutes), a maximum concentration approximately twice higher than regular human insulin, a maximum glucose lowering effect from 1 to 3 h, lasting for 3 to 5 h (vs 5 to 8 h) [75]. Amount of subcutaneous absorption is independent of the site of injection, but as usual, absorption is faster after abdominal than after thigh injection [76]. Absorption of insulin aspart is not influenced by the dose [72] and does not seem influenced by BMI (range 19-39 kg/m²) in a healthy volunteer study [77]. In healthy volunteers, the mean intra-individual and inter-individual CV of the main pharmacokinetic parameters were lower after subcutaneous injection of insulin aspart than after the same dose of regular human insulin, mean intra-individual CV was 15% (vs 24%, p < 0.05) for the time to the peak of insulin (t max) and the mean inter-individual CV were 20% (vs 37%, p < 0.05) for t max and 18% (vs 28%, p < 0.001) for the insulin concentration at t max [78]. But the mean inter-individual and inter-individual CV of pharmacodynamic parameters were comparable for both insulins, ~ 25% for intra-individual CV and 30% to 50% for inter-individual CV, although with insulin aspart the inter-individual CV was significantly lower for several main pharmacodynamic parameters derived from GIR, as the time to maximal GIR (mean inter-individual CV = 19% vs 23%, p < 0.001) [78]. Similarly, in type 1 diabetic patients, there was less variability in post-prandial glucose levels for 2 or 3 meals over 24 hours after insulin aspart than after regular human insulin [74].

Insulin glulisine

The structure of insulin glulisine is similar to human insulin except for an asparaginase to lysine substitution at position B3, and a lysine to glutamine acid substitution at insulin except for an asparaginase to lysine substitution at position B3, and a lysine to glutamine acid substitution at position B3, and a lysine to glutamine acid substitution at position B3, and a lysine to glutamine acid substitution at position B3, and a lysine to glutamine acid substitution at position B3. Few published data are available so far. Comparative pharmacokinetic and pharmacodynamic (euglycemic clamp) studies with insulin glulisine vs insulin lispro and regular conventional insulin indicate that insulin glulisine and insulin lispro were very similar in these respects [79, 80]. Comparison of the effect of different subcutaneous injection sites (femoral, deltoïd or abdominal areas) on the pharmacokinetics, pharmacodynamics (GIR during an euglycemic clamp) and absolute bioavailability of insulin glulisine showed similar effects regardless of the site of injection, although as usual, the abdominal route was associated with more rapid insulin delivery [81]. No data on variability are published yet, but intra-subject variability with insulin glulisine was reported to be comparable to insulin lispro and regular human insulin [80].

Long-acting insulin analogs

Two long-acting analogs are currently available (glargine) or will be soon (levevirm, approved in June 2004 by the European Medical Agency). They are presented as clear neutral solution, thus eliminating variability dependent on appropriate resuspension before injection and dissolution of crystals in the subcutaneous tissue. Insulin glargine [review in 82-84]

This insulin analog is produced by substituting asparagine with glycine in position A21 and by adding 2 arginine-molecules on positions B31 and B32 of the human insulin molecule. These modifications led to a shift of the iso-electric point from 5.4 in native insulin to 6.7, making glargine a soluble insulin preparation at a slightly acidic pH and a less soluble one at physiological levels. Small amounts of zinc have been added to this formulation to further extend its absorption time. After injection, insulin glargine precipitates in the physiologic, neutral pH of subcutaneous tissue which delays its absorption and prolongs its duration of action. Moreover, insulin glargine forms hexamers that are more stable and more dense than those of human insulin. However, as insulin glargine forms an amorphous microprecipitate at the site of subcutaneous injection, this may affect the rate of dissolution and absorption from this site and therefore influence the variability of insulin glargine action [26]. Comparative pharmacokinetic and pharmacodynamic studies demonstrated that insulin glargine is peakless and 50% lower and the duration of activity twofold longer than observed with NPH. The rate of absorption of insulin glargine provides a basal plasma insulin level which remains constant for at least 24 hours. The mean time to onset of action is 1.5 hours (compared to 0.8 h for insulin NPH), the metabolic effect increased to a plateau within 4 hours and then remained rather constant throughout the 24-h period following the subcutaneous injection with a constant concentration/effect vs time profile for at least 22 hours [82, 83]. Of a particular interest is the study conducted by Lepore et al. [61] to compare the pharmacokinetics/dynamics of insulin glargine with NPH and ultra-lente insulins and with a continuous subcutaneous infusion of insulin (CSI) using insulin lispro, in 20 type 1 diabetic patients who were studied on four occasions during an isoglycemic 24-h clamp. In this study, inter-individual variability calculated as differences in SD of plasma insulin concentrations was comparable to NPH and CSI, and less than for ultralente insulins, but when assessed as differences in SD of GIR over 24 hours (24 time-points during the study), the inter-individual variability was lower for insulin glargine (and comparable to CSI) than for NPH and ultralente insulins. Globally, in this study, insulin glargine had a lower intersubject variability than NPH (and indeed as expected than ultralente) and was similar to that of CSI. Table I presents the main pharmacodynamic results of this study [61]. Another study, but in healthy volunteers showed similar results, variability for insulin glargine and
Comparative pharmacodynamics of subcutaneous injection of insulins glargine, NPH and ultralente (0.3 U/kg), and of continuous subcutaneous infusion of insulin lispro [CSII] (0.3U * kg⁻¹ * 24 h⁻¹) in 20 type 1 diabetic patients studied on four occasions during an isoglycemic 24-h clamp. Intersubject variability of plasma insulin concentrations and of glucose infusion rates (GIR) were calculated from the standard differences (SD) of the 24 time-points during the study. All data as mean ± SE [adapted from ref. 61].

<table>
<thead>
<tr>
<th>Pharmacodynamics:</th>
<th>Glargine</th>
<th>NPH</th>
<th>CSII</th>
<th>Ultralente</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action (h)</td>
<td>1.5 ± 0.3</td>
<td>0.8 ± 0.2*</td>
<td>0.5 ± 0.1*</td>
<td>1.0 ± 0.2*</td>
</tr>
<tr>
<td>End of action¹ (h)</td>
<td>22 ± 4</td>
<td>14 ± 3*</td>
<td>24 ± 0*</td>
<td>20 ± 6</td>
</tr>
<tr>
<td>Duration of action (h)</td>
<td>20.5 ± 3.7</td>
<td>13.2 ± 2.8*</td>
<td>23.5 ± 0*</td>
<td>19.0 ± 5.8*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intersubject variability:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- SD of plasma insulin (µU/ml)</td>
</tr>
<tr>
<td>- SD of GIR (mg * kg⁻¹ * min⁻¹)</td>
</tr>
</tbody>
</table>

¹ Defined as an increase of plasma glucose > 150 mg/dL.
NR: exact value not reported, mean value estimated from graphs.
Pharmacodynamics of action: * p < 0.05 (vs glargine).
Intersubject variability: * p < 0.05 (glargine vs NPH or CSII vs ultralente); ** p < 0.001 (CSII vs ultralente).

NPH was comparable and significantly lower than with ultralente insulin, when comparing between-day (absolute) differences in various variables derived from serum insulin concentrations and GIR; when the comparisons of between-day differences was assessed by individual SD of diurnal between-day differences between these same variables, it was found that, in average, there was 30-50% less variation for insulin glargine GIR profiles as compared with NPH and ultralente insulins, although 2 of the 12 subjects had non-reproducible profiles [85]. When the pharmacodynamic activity was evaluated using an isoglycemic clamp technique after the first and the seventh dose of insulin glargine subcutaneously at bedtime, the results obtained on day 7 (more likely to reflect insulin activity at steady state) showed a lower interindividual variability and a more constant within-patient glucose-lowering effect than after day 1 (p < 0.05) [86]. Altogether, these studies confirm there may be inter- and intra-individual variation in the time profile of pharmacodynamic activity of insulin glargine [83]. In 12 healthy volunteers, the absorption rate showed no significant variation between injection sites [42], however this is subject to discussion as the mean values for 25% disappearance were very different, although not statistically significant, suggestive of a high variability masking inter-site differences [87]. A study to assess the effect of exercise on the absorption of insulin glargine was conducted in 13 type 1 diabetic patients, intense 30-minutes period of exercise does not significantly increase the absorption rate of I-labelled insulin glargine injected subcutaneously into the thigh, although the variability in insulin levels was greater (ΔAUCinsulin: − 2.1 ± 3.9 pmol non-exercise vs 1.5 ± 6.2 pmol exercise), the insulin levels (ΔAUC insulin) did not differ significantly when comparing exercise vs non-exercise, which demonstrate the absence of effects of intense exercise on the absorption rate and pharmacokinetics of subcutaneously injected insulin glargine [88].

Insulin detemir [review in 89]

The prolonged duration of action of detemir is attributable to a combination of increased self-association (hexamer stabilisation and hexamer-hexamer interaction) and albumin binding due to acylation of the amino-acid lysine in position B29 with a 14C fatty acid (myristic acid). Pharmacokinetic and clinical studies have demonstrated a protracted metabolic action, with a slow onset of action, a less pronounced peak concentration nearly 90 minutes later and a flatter time-action profile compared with that observed for NPH insulin [89-92]. These properties translate in reduced variability in glycemic values, and moreover, in more constant nocturnal glucose profiles with a significantly reduced risk of nocturnal hypoglycemia than after NPH insulin. In contrast to NPH insulin, treatment with insulin detemir was not usually associated with increases in bodyweight in patients with type 1 diabetes and was associated with significantly less bodyweight gain than NPH insulin in type 2 diabetic patients [89-92].

The pharmacokinetic and pharmacodynamic responses (glucose-lowering time-action profile) was studied in 12 people with type 1 diabetes who were given single subcutaneous injections of insulin detemir in a range of doses (from 0.1 to 1.6 U/kg). The dose-response relationships were linear and dose-dependent for both pharmacokinetic and pharmacodynamic measures. The mean duration of action was 12 h at a dose of 0.2 U/kg, 20 h at a dose of 0.4 U/kg (a typical therapeutic dose) and exceeded 24 h at the highest dose of 1.6 U/kg [93]. This suggests that many patients will be able to dose detemir once daily according to the dose needed [31].

Three euglycemic clamp studies were conducted in type 1 diabetic patients and all of them have shown that insulin detemir provides a consistent, predictable and protracted effect on blood glucose with a lower degree of intrapatient...
variability compared with NPH insulin [93-95] or insulin glargine [95]. The largest study [95] included 54 type 1 diabetics, each of them received four single subcutaneous doses of 0.4 U/kg of either insulin detemir (n = 18), insulin glargine (n = 16) or human NPH insulin (n = 17) under euglycemic clamp (target blood glucose 5.5 mmol/l). The pharmacodynamic (GIR) and pharmacokinetic (serum concentrations of the respective insulins) properties were recorded for 24 h postdosing. Insulin detemir was associated with significantly less within-subject variability than both NPH and glargine insulins, as assessed by the CV for the various pharmacodynamic end-points: GIR-AUC_{(0-12h)}, GIR-AUC_{(0-24h)} and GIR-AUC_{(2-24h)} (areas under the GIR profile in the time intervals from 0 to 12 h, from 0 to 24 h and from 2 to 24 h postdosing), and GIRmax (maximum GIR), p < 0.001 for all comparisons, as presented in Table II. GIR-AUC_{(2-24h)} may represent a more valuable end-point of the true long-acting insulin effect, as it excludes the period of action of a short-acting insulin analog these patients will inject in clinical situation.

Significant reductions in the day-to-day within-subject variability of self-measured fasting blood glucose levels (calculated from SD of blood glucose) with insulin detemir compared with NPH insulin have been consistently found in all clinical trials conducted so far [89, 96-98]. This lower within-subject variability was found whatever the insulin detemir regimen was. It was confirmed in a meta-analysis of continuous blood monitoring data pooled from 5 multinational, randomised, non-blind phase III trials in type 1 or type 2 diabetic patients in comparison to NPH insulin. Variability in blood glucose levels was expressed by the estimation of fluctuations and excursions recorded with a MiniMed CGMS® worn by subgroup of patients for 72 h during the last month of the treatment’s trial. Fluctuation was defined as the area between the blood glucose curve and the subjects individual average blood glucose level from 11:00 pm to 06:00 am (nocturnal), or over 24 h. Similarly, excursion was defined as the area where blood glucose was outside the desired blood glucose range (4-10 mmol/l). This lower within-subject variability, was confirmed whatever the insulin detemir regimen was, i.e. either morning and before dinner or morning and bedtime, together with insulin aspart in basal-bolus therapy for type 1 diabetes, or as an add-on therapy morning and evening in combination with oral antidiabetic agents in type 2 diabetic patients [99]. Table III presents the results of this meta-analysis on nocturnal and 24-hour fluctuations and excursions. This reduced within-subject variability may be attributed to the soluble formulation and unique method of protraction of insulin detemir [96].

Reducing insulin variability: consequences and benefits

Clinical consequences and benefits

Short (rapid)-acting insulin analogs were demonstrated to have similar efficacy to conventional regular insulin, but there subcutaneous absorption is 2-3 times faster, peak concentration is higher and is reach earlier (within half the time) with a return to baseline level within 4-5 hours. As their onset of action occurs generally within 15 minutes and their

<table>
<thead>
<tr>
<th>Pharmacodynamics:</th>
<th>Insulin detemir (n = 18)</th>
<th>NPH insulin (n = 17)</th>
<th>Insulin glargine (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIR-AUC_{(0-12h)} (mg/kg)</td>
<td>27</td>
<td>59*</td>
<td>46*</td>
</tr>
<tr>
<td>GIR-AUC_{(0-24h)} (mg/kg)</td>
<td>27</td>
<td>68*</td>
<td>48*</td>
</tr>
<tr>
<td>GIR-AUC_{(2-24h)} (mg/kg)</td>
<td>27</td>
<td>77*</td>
<td>66*</td>
</tr>
<tr>
<td>GIR_{max} (mg.kg^{-1}.min^{-1})</td>
<td>23</td>
<td>46*</td>
<td>36*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacokinetics:</th>
<th>Insulin detemir (n = 18)</th>
<th>NPH insulin (n = 17)</th>
<th>Insulin glargine (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INS-AUC_{(0-12h)} (nmol · min^{-1} · l^{-1})</td>
<td>15</td>
<td>26</td>
<td>34</td>
</tr>
<tr>
<td>INS-AUC_{(0-24h)} (nmol · min^{-1} · l^{-1})</td>
<td>14</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>C_{max} (pmol/l)</td>
<td>18</td>
<td>24</td>
<td>34</td>
</tr>
</tbody>
</table>

* p < 0.001 vs insulin detemir.

GIR-AUC_{(0-12h)}, GIR-AUC_{(0-24h)} and GIR-AUC_{(2-24h)}: areas under the glucose infusion rate (GIR) curve in the time intervals from 0 to 12 h, 0 to 24 h and from 2 to 24 h post-dosing.

GIR_{max}: maximum GIR.

INS-AUC_{(0-12h)} and INS-AUC_{(0-24h)}: area under the curve of insulin in the time intervals from 0 to 12 h and from 0 to infinite.

C_{max}: maximal insulin concentration.
action is shorter, their use is more suitable and comfortable for patients. They can be injected immediately before meal, without the need for a between-meal to counter a prolonged hyperinsulinemia. Clinical studies have not shown an increased frequency of hypoglycemia compared with regular human insulin, despite equivalent or improved 1-hour and 2-hour post-prandial glycemic control [32, 67, 74]. Of a particular interest, when used in a basal-bolus regimen before meals, with NPH insulin as basal insulin once- or twice-daily, nocturnal hypoglycemia were markedly reduced [32, 100], as well as severe hypoglycemia (requiring external/third-party assistance) reduced by 20-30% [26]. Additionally, their pharmacokinetic properties permit to correct more effectively than with regular human insulin, incidental hyperglycemia in patients receiving multiple injection therapy [101], or hyperglycemia during intercurrent acute illness [26], by the injection of a small additional dose (2-4 U) of short-acting analog. This means that such short-acting insulin analogs that allow a more physiological replacement of mealtime insulin secretion are particularly suitable for intensive-insulin therapy, assuming an optimization of basal insulin regimen [26, 32, 100].

Conventional intermediate and long-acting insulin have major pharmacokinetic and pharmacokinetic defects: in contrast to the physiological needs, they show an early peak 4-5 h after the subcutaneous injection, followed by a rapid waning of action. This translates in frequent hypoglycemia in the early night hours, even despite a bedtime snack, and a lack of effect in the late part of the night/early morning when hepatic requirements are greater and fasting blood glucose increased. Any attempt to correct this “dawn phenomenon” by increasing the evening insulin dose, increases the risk of nocturnal hypoglycemia rather than improving nocturnal blood homeostasis [26]. Finally, the large intra- and inter-patient variability seen with these conventional intermediate and long-acting human insulins, further reinforce patient’s fear of hypoglycemia, favours a less strict glucose control, and complicates physician’s task [26, 32]. In type 1 diabetics, clinical studies with long-acting analog insulin (either glargine or detemir) by comparison to NPH regimen, have consistently shown a similar or a modest improvement in glycemic control, a risk of hypoglycemia similar to or lower than that of NPH insulin, but with a significantly reduced incidence (sometimes 50% lower) of nocturnal hypoglycemia [83, 84, 89, 100].

Taken together, data on the use of short-acting and long-acting insulin analogs demonstrate they provide better glycemic control (lower HbA1c, less day-to-day variability in plasma glucose, less hypoglycemics with preserved awareness of, and counterregulation to, hypoglycemia) and a more friendly use by diabetic patients. The reduced incidence of hypoglycemia is of a particular importance: fear of hypoglycemics by patients and healthcare professionals mean a less strict glucose control in insulin-treated patients and a too long delay to initiate insulin therapy in type 2 diabetics when oral antidiabetic agents fail, possibly less weight gain when on insulin. Lower hypoglycemia event rates mean a reduction in the cost increase associated with their treatment and management as well as in the cost of long-term diabetic complications associated to an insufficient glucose control [102]. Furthermore, available data suggest that amongst patients with comparable HbA1c, those with larger glucose fluctuation (hyper-/hypoglycemics) within the day and from day-to-day may be exposed to a greater risk of diabetic complications through a qualitative biological defect due to glucose instability [103].

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**Table III**

Within-patients variability in blood glucose levels with insulin detemir in comparison to NPH insulin. Results of a meta-analysis of nocturnal and 24-hour continuous blood glucose profiles from 5 phase III trials in type 1 and type 2 diabetic patients. Blood glucose levels were recorded from subgroups of patients who wore the MiniMed Continuous Glucose Monitoring System (CGMS) for 72 h during the last month of treatment. Variability was assessed by estimation of fluctuations (defined as the area between the blood glucose curve and the patients individual average blood level from 11:00 pm to 06:00 am [nocturnal], or over 24 h) and excursions (defined as the area where blood glucose was outside the desired range 4-10 mmol/l) with each treatment [adapted from ref. 99].

<table>
<thead>
<tr>
<th></th>
<th>Insulin detemir (mean)</th>
<th>NPH insulin (mean)</th>
<th>Detemir-NPH Mean difference 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nocturnal:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluctuation</td>
<td>8.79</td>
<td>9.97</td>
<td>-1.18 [-1.86; -0.51]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Excursion &lt; 4 mmol/l</td>
<td>0.82</td>
<td>1.08</td>
<td>-0.25 [-0.49; -0.01]</td>
<td>0.04</td>
</tr>
<tr>
<td>Excursion &gt;10 mmol/l</td>
<td>4.4</td>
<td>4.82</td>
<td>-0.42 [-1.46; 0.63]</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>24-hours:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluctuation</td>
<td>48.73</td>
<td>53.74</td>
<td>-5.01 [-8.15; -1.87]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Excursion &lt; 4 mmol/l</td>
<td>2.15</td>
<td>2.63</td>
<td>-0.48 [-1.02; 0.05]</td>
<td>0.08</td>
</tr>
<tr>
<td>Excursion &gt;10 mmol/l</td>
<td>12.99</td>
<td>15.17</td>
<td>-2.18 [-5.06; 0.70]</td>
<td>0.14</td>
</tr>
</tbody>
</table>
Towards an optimization of insulin regimen

Use of short-acting and long-acting insulin analogs will permit to optimize insulin regimen towards a near-normoglycemia in type 1 diabetic patients (and in type 2 diabetics when intensive insulin treatment is deemed necessary). Studies with the long-acting insulin analogs glargine and detemir have demonstrated their action profile, flatter and longer than that of NPH insulin, translates in reduced fasting blood glucose and in a decreased risk of hypoglycemia, particularly nocturnal hypoglycemia. Low variability observed with insulin detemir may be an unique advantage over insulin glargine, but comparative clinical trials to confirm if these pharmacokinetic and pharmacodynamic advantages translate into benefits on clinical outcomes have still to be conducted. Nevertheless, a larger number of patients with type 1 diabetes and increasing numbers of type 2 patients are now treated with intensified insulin therapy and receive a “basal-bolus” regimen. However in France, the number of patients treated with an optimized basal-bolus regimen remain limited. In the SCHEMA survey [105] conducted in 1998 among 450 of all 1,353 registered diabetologists/endocrinologists, about 17% of their 1,263 insulin-treated diabetic patients were receiving a “basal-bolus” regimen. A more recent survey (the ARAMIS registry) [106], conducted between October 2003 and March 2004 (by the time of insulin glargine launch), showed the use of such “basal-bolus” regimen in 24% of the 922 type 1 diabetic patients from 245 nationwide diabetologists, an increased, but relatively modest, use since the 1998 SCHEMA survey. If in patients properly educated, short-acting insulin analog may represent an adequate response to post-prandial blood glucose rise, it is hoped that improvement in variability of effect with basal insulin should benefit the glucose control and the acceptability and compliance to these regimens [100]. The recently reported study by Hermansen et al. [97], conducted in parallel group in 595 type 1 diabetic patients randomised either to insulin analogs (insulin detemir and insulin aspart) or to conventional human insulins (NPH insulin and regular human insulin) as basal-bolus therapy, has demonstrated an improved glycemic control (HbA1c: 7.88% vs 8.11%; mean difference: –0.22% point [95% CI: –0.34 to –0.10]; p < 0.001) and a significant reduction in the risk of overall (21% reduction, p = 0.036) and nocturnal hypoglycemia (55% reduction, p < 0.01), without concomitant weight increase with the insulin detemir/insulin aspart basal-bolus regimen in comparison to the NPH insulin/regular human insulin combination. This study underlines the clinical benefits generated by new insulin analogs with a more physiological action profile.

Functional intensified insulin therapy: a new approach?

Another approach permitted by insulin analogs in type 1 diabetic patients is the concept of “functional intensified insulin therapy” [107] which aims to facilitate the patient’s life and to “mimic” physiological β-cell secretion. It consists in the association of a low “basal” dose (0.3-0.4 UI/kg) of long-acting insulin (either NPH twice-daily or insulin glargine once daily) to a short-acting “prandial” insulin with a dose determined according to the post-prandial glucose target, the carbohydrate content of the meal and the pre-prandial blood glucose. Insulin detemir use and benefit have not been tested in these conditions yet.

Towards an earlier insulin therapy initiation in type 2 diabetic patients

In type 2 diabetic patients, when oral antidiabetic agents fail, initiation of insulin therapy is generally delayed due to various barriers: patients’ fear of disease progression and needle anxiety, patients’ and healthcare professionals’ concerns on hypoglycemia and weight gain, health professionals’ use of insulin as a threat to encourage compliance with diet and oral therapies, etc. [8, 108-110]. Insulin regimen in these patients was, for a long-time, a matter of debate [111-114]. Traditionally, insulin therapy is initiated as a once- or twice-daily injection of NPH insulin, this is convenient for the patient as it involves few injections, but it does not target post-prandial glucose control. Clinical studies with either insulin glargine once-a-day [115] or insulin detemir twice-a-day [116], in combination with oral agents, have consistently demonstrated a significant improvement in glycemic control, with a reduced variability and significantly less nocturnal hypoglycemia by comparison to traditional NPH therapy. The “ Treat-to-Target” trial [117] was a key-study in this respect. This study has compared the effects of insulin glargine and human NPH insulin added to oral therapy of 756 overweight type 2 diabetic patients inadequately controlled on one or two oral antidiabetic agents, and it was demonstrated that systematically titrating bedtime basal insulin added to oral therapy can permit to safely achieve the 7% HbA1c objective in a majority of patients with both insulins, but with significantly less nocturnal hypoglycemia with the long-acting insulin analog glargine than NPH, thus...
reducing a leading barrier to initiate insulin sooner in type 2 diabetic patients. Since the publication of these “Treat-to-Target” trial results, a large consensus exists to propose a long-acting insulin analog as the basal insulin, injected either at breakfast, dinner or bedtime, and to educate the patients to obtain a tight glycemic glucose control in the morning (below 1.0 g/l [5.6 mmol/l]), whatever is the insulin dose needed, even when largely increased [27, 118-121]. The fact that insulin detemir was associated with significantly less bodyweight gain than NPH insulin in type 2 diabetic patients [89, 116, 122] may be a further advantage towards an earlier insulin initiation. Benefits of insulin detemir administered once-daily as an add-on to oral agents in type 2 diabetic patients remain to be studied.

Consequently, use of long-acting insulin analog may facilitate an earlier and effective management of type 2 diabetic patients, even with the possibility to initiate insulin on an outpatient basis in primary care, a procedure which will permit to decrease cost of diabetes care [123, 124]. However such ambulatory practice will require specific training and education for selected general practitioners and a different health care system organization [125]. Other approaches may be envisaged also, as the proposed earlier use of small bolus of short-acting insulin to control post-prandial hyperglycemia in patients treated with oral antidiabetic agents.

**Perspectives**

Use of insulin in type 2 diabetic patients appears lower in France than in other European countries where they are generally reported to represent 24% to 30% of all treated type 2 diabetics. Although the percentage of all insulin-treated diabetics in France is increasing steadily, it is currently estimated (based on data from the National Health Insurance System, CNAMTS) that about 16.3% of all pharmacologically-treated diabetics were using insulin, either insulin in combination with oral antidiabetic agents or insulin alone, i.e. approximately 447,000 individuals, 70.6% of them being type 2 diabetic patients [126]. In the French National Health Surveillance program (ENTRED), a prospective survey of 10,000 diabetic patients (80.0% of them type 2 diabetics) reimbursed from diabetes medical treatments during the 4th quarter 2001, it was estimated that 5.9% were treated with a combination of insulin and oral antidiabetic agents and 14.1% with insulin alone [127].

Among type 2 diabetic patients, the percentage of insulin-treated (either alone or in combination with oral antidiabetic drugs) increased from 12.3% to 16.5% between 1998 and 2002, i.e. a mean increase of 7.4% per year [126]. However considerable differences exist when considering patients treated by general practitioners (GP) or by specialists (diabetologists/endocrinologists, SPE). In the ECODIA survey [128] conducted between December 1998 and April 1999, 4,119 type 2 diabetic patients were enrolled by 311 GP and 51 SPE randomized from national files of practitioners, among these type 2 patients, only 5.8% of those treated by GP were receiving insulin (with/without oral antidiabetic agents) vs 11.5% of those treated by SPE. The more recent nationwide ESPOIR survey [129] was conducted from October 2000 to July 2001, 410 SPE enrolled 4,930 type 2 diabetic patients, 18% of them being treated by insulin and oral antidiabetics and 9% by insulin alone. In another recent study, DIASTEP [130], a prospective study aimed to improve management of type 2 diabetic patients through regular training and corrective actions implemented into GP’s practice, 1,631 GP enrolled more than 15,000 type 2 diabetic patients in 2001, 8.7% of these patients being treated with insulin (either alone or in combination with oral antidiabetes), a percentage increased to 9.2% one year later after implementation of the training program.

However, glucose control in this patient’s population is generally considered as less than satisfactory. In the “SCHEMA Survey” [105] conducted in 1998 among 1,263 insulin-treated diabetics managed by SPE, Hba1c was < 7.5% in only 30% of the type 1 patients and in 35% of those with type 2 diabetes, about 40% of the type 2 diabetics having Hba1c ≥ 8.5%. In more recent studies, such as the ESPOIR survey [129], Hba1c was ≤ 6.5% in less than 15% of all insulin treated type 2 diabetics and was > 8% in more than 40% of them. Although the results of these various surveys may reflect differences in the clinical situation and severity of diabetes managed by GPs or by SPE, clearly control of diabetes is far to be optimal in a large number of type 2 diabetic patients [126, 129].

It is hoped that use of insulin analogs with improved pharmacokinetic and pharmacodynamic properties, a more reproducible and predictive action, and thus a reduced risk of hypoglycemic events and an easier and more confident use by patients and healthcare professionals, will permit an improvement in the management of glucose control in both type 1 and type 2 diabetic patients, as illustrated by the improvement in the 1-year Hba1c of type 2 diabetic patients with in-hospital basal insulin initiation when their oral antidiabetic agents fail (IDAHO-2 registry) [131].

However, these therapeutic improvements will translate in an improved management of glucose control only if a parallel improvement is achieved in glucose-sensing technologies available to the patients, permitting them an easy, safe and optimal self-management of their insulin therapy and diabetes [100], as well as in a better awareness of the importance of glucose control and an appropriate training, funding and support at all levels, including general practitioners [114, 126].

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