

Variability of Insulin Action: Does It Matter?

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ABSTRACT

Background: Repeat SC injection of identical insulin doses does not induce an identical metabolic effect in patients with diabetes. This concept hampers practical insulin therapy tremendously.

Objective: The aim of this article is to briefly and critically review the available literature on the variability of insulin action.

Methods: There are only limited numbers of clinical-experimental and clinical studies focusing on the variability of insulin action; therefore, no formal literature search was performed. However, the available studies, along with their references, provided the basis for our findings.

Results: Insulin absorption from the SC depot is mainly determined by local blood flow, and many factors affect blood flow. The metabolic effect of absorbed insulin depends on a patient's insulin sensitivity, which is highly variable both intraindividually and interindividually. SC injection of prandial insulin shows an intraindividual coefficient of variation (CV) of insulin action of 15% to 25% and an interindividual CV of 20% to 45% under experimental conditions. The intraindividual variability of insulin action for intermediate-acting/basal insulin is not much higher at 25% to 35% than that of prandial insulin. The variability of the currently available soluble long-acting insulin analogues is reduced compared with neutral protamine Hagedorn insulin in most but not all studies. Although other routes of insulin application (eg, inhalation) might provide an opportunity to reduce the variability of insulin action, the intraindividual variability of metabolic effect observed after inhalation of insulin (15%–30%) was comparable to that seen after SC administration of prandial insulin (15%–25%).

Conclusions: The variability of insulin action is clinically highly relevant; however, an intensive scientific investigation of this topic is lacking. Nonetheless, this research might well enable the development of insulin formulations or insulin application techniques that would help reduce this disturbing aspect of insulin therapy. (*Insulin*. 2008;3:37–45) © 2008 Excerpta Medica Inc.

Key words: insulin, prandial insulin, basal insulin, insulin therapy, inhalation, variability, pharmacodynamics, pharmacokinetics.

INTRODUCTION

The metabolic effects induced by injection of identical doses of insulin into the SC depot varies considerably both intraindividually and interindividually. Clearly, it is the intraindividual variability of insulin action that is of relevance for the treatment of patients with diabetes. The inherent variability of insulin action considerably hampers the establishment of a reproducible insulin therapy, as it is a source of glucose variability. A consequence of such acute swings in glycemia is an increased risk of hypoglycemic events. Patients with diabetes often fear hypoglycemic events and therefore tend to avoid higher insulin doses. Suboptimal dosing might promote acute metabolic deteriorations, which, in turn, represents a major barrier to achieving optimal glycemic control.

It has become evident that this variability is disturbing to patients not only because it contributes to unpredictable swings in blood glucose levels but also because it appears to

have an impact on their long-term prognosis.¹ Surprisingly, this well-known characteristic of variability was not investigated until recently, and many factors influencing the variability of insulin action are still poorly understood. Whereas many studies focus on the effects of glucose variability, only a few focus on the underlying reasons for this variability. Quite interestingly, and disturbingly, only a limited number of studies have investigated the variability of insulin action as it pertains to continuous SC insulin infusion, employing up-to-date pumps and insulin formulations.

It would be interesting to know the intraindividual variability of insulin action observed after repeated applications of a prandial insulin bolus by means of an insulin pump. Would this variability be comparable to or lower than that observed with SC insulin injection of the same insulin formulation and dose? One can speculate that the absorption properties from the insulin depot around the tip of the infusion catheter differ from those of the insulin depot of a SC injection.

MATERIALS AND METHODS

There are only limited numbers of clinical-experimental and clinical studies focusing on the variability of insulin action; therefore, no formal literature search was performed. However, the available studies, along with their references, provided the basis for our findings.

SOURCES OF VARIABILITY

Major contributors to the variable metabolic effect of insulin are *changes in the absorption rate* of insulin into the bloodstream (pharmacokinetic aspect) and the *metabolic effects* induced by circulating insulin in insulin-sensitive tissues (pharmacodynamic aspect). The intraindividual and interindividual variability of insulin action and insulin absorption of various insulin formulations are described in **Table I**.²⁻¹⁰

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One factor key to the insulin absorption rate is the local blood flow near the insulin depot in SC tissue. This blood flow determines insulin absorption from the depot across the capillary membrane into the bloodstream. It is well known that a variety of factors have an impact on the local blood flow (**Table II**).¹¹ However, a closer look reveals that our knowledge about these factors and to what extent they contribute quantitatively to the variability of insulin absorption is still limited. Most likely, it is the sum of all or most of these factors and their interactions that makes insulin absorption after SC administration so erratic.

The variability of insulin absorption cannot be considered equivalent to the variability of insulin action. If it were, this would mean that, after absorption into the bloodstream, insulin would always elicit a stereotypic metabolic effect in the body in terms of quantity and time. However, even identical insulin concentrations in the blood, as can be effected in a clinical-experimental setting by means of an IV insulin infusion, do not elicit identical glucose-lowering effects. Depending on the current level of insulin sensitivity in an individual patient, the metabolic effect induced can vary widely. A number of factors influence insulin sensitivity acutely or chronically. Physical activity can modify insulin sensitivity relatively rapidly (ie, acutely), whereas certain drugs or the level of metabolic control can have a long-term (ie, chronic) effect on insulin sensitivity. Cortisone therapy, for example, greatly reduces insulin sensitivity. Changes in insulin sensitivity also contribute to the intraindividual variability of insulin action in patients with diabetes; however, these changes do not necessarily increase variability. Thus,

the variability of insulin absorption is less than that of insulin action, as the 2 sources of variability equal out. The following section focuses on the variability of insulin action and insulin absorption, as it is the total variability that is meaningful for our patients.

HOW TO MEASURE AND DESCRIBE VARIABILITY OF INSULIN ACTION

The first investigation to describe the variability of insulin absorption in quantitative terms in healthy subjects and patients with diabetes dates from 1959.¹² In this study, as in most studies of the subsequent period, it was not the variability of insulin action that investigators studied, but the variability of insulin absorption from SC adipose tissue.

The most reproducible approach to measure variability of insulin action is the euglycemic glucose-clamp technique. By keeping blood glucose constant at the target level through varying the rates of an IV glucose infusion appropriately, registration of the amount of infused glucose reflects the metabolic effects of the subcutaneously injected insulin. Repeating this experimental procedure several times while applying an identical insulin dose/insulin formulation in the same subjects is the best method to quantitatively determine the variability of insulin action. However, intercenter variability of the exact manner in which glucose clamping is performed has an impact on the outcome of such studies; for example, is the clamping performed manually, with more or less frequent measurements of blood glucose and manual adjustments of the glucose infusion rates, or is it performed automatically by means of a glucose-controlled insulin infusion system? Moreover, the site of insulin injection has an impact not only on the time-action profile but probably also on the variability of insulin action. No appropriate study comparing the variability of action after repeated injections at different sites has been performed.

One also has to acknowledge the limited reliability of the glucose-clamp technique in measuring the insulin effect quantitatively under highly artificial circumstances. Subjects must remain practically motionless in bed for >16 hours without regular meals, which, in turn, also has an impact on insulin sensitivity. In the daily life of patients with diabetes, other factors (eg, exercise) most probably lead to an even greater variability of insulin action.

Different statistical approaches are used to describe the variability of insulin action. The simplest approach is to calculate the coefficient of variation ($CV = [SD/mean] \times 100$) for certain pharmacodynamic summary measures. This approach is also called the "average of ratios." More recently, different models of analysis of variance (ANOVA) have been used to analyze variability of insulin action. It appears that by calculating the average of ratios, the intraindividual variability is underestimated compared with the ANOVA approach, which appears to be more reliable. In detail, some differences also exist among the various ANOVA methods, which also appear to have an impact on the outcome of cal-

Table 1. Intraindividual and interindividual variability of insulin action (pharmacodynamic parameters) and insulin absorption (pharmacokinetic parameters).*

Pharmacodynamic parameter*	Subcutaneous Insulin					Inhaled Insulin				
	Regular Insulin ²	Regular Insulin ³	NPH Insulin ⁴	Lente Insulin ⁴	NPH Insulin ⁵	NPH Insulin ⁶ (95% CI)	Astra ^{7†}	Aradigm ^{8‡}	PDC ^{9§}	AeroGen ¹⁰
GIR _{max}	—	15 (7) [26]	—	—	29 (27) [42]	23 (13, 33)	14 (9)	—	36 (20)	—
T _{max}	—	14 (10) [23]	—	—	26 (33) [49]	—	15 (10)	—	21 (15)	—
Early T _{50%}	—	16 (10) [25]	—	—	25 (29) [81]	11 (6, 17)	28 (33)	—	—	—
Late T _{50%}	—	19 (9) [26]	—	—	12 (16) [28]	—	17 (12)	—	—	—
AUC _{0-2/3/4 h}	—	27 (22) [44]	—	—	46 (53) [54]	—	13 (8)	—	32 (16)	19
AUC _{0-8/10/24 h}	22.6 [51.3]	13 (3) [21]	—	35.1 [44.8]	35 (33) [50]	22 (12, 32)	16 (12)	34.2	30 (17)	21
Pharmacokinetic parameter*										
C _{max}	—	19 (8) [28]	46.6	39.0 [44.3]	18 (20) [23]	21 (12, 31)	19 (7)	—	29 (14)	—
T _{max}	—	24 (10) [37]	68.1	51.4 [54.5]	42 (33) [61]	36 (20, 52)	25 (12)	—	22 (15)	—
AUC _{0-2/3/4 h}	—	19 (8) [31]	—	—	30 (30) [34]	—	17 (6)	—	25 (11)	19
AUC _{0-8/10/24 h}	11.2 [18.1]	14 (10) [17]	—	44.1 [45.9]	18 (18) [28]	19 (11, 28)	19 (6)	25.8	23 (9)	22

NPH = neutral protamine Hagedorn; GIR = glucose infusion rate; T = time; T_{50%} = time to half-maximal metabolic activity before or after maximal metabolic activity was reached.

*Values are given as % intraindividual coefficient of variation (CV) after SC injection of regular and NPH insulin or after inhalation of insulin. Data are mean or mean (SD) values and were obtained in different studies. Interindividual CVs are in brackets. AUC was calculated for different time intervals.

†Astra, Lund, Sweden.

‡Aradigm Corporation, Hayward, California.

§Pharmaceutical Discovery Corporation, Danbury, Connecticut.

||AeroGen, Inc., Sunnyvale, California.

Table II. Factors known to influence absorption and action of subcutaneously injected insulin.

Insulin Preparation	Differences Between Injection Sites	Changes on Injection Site*
<ul style="list-style-type: none"> • Galenic principle of protraction • Dose • Physical status (solution or suspension) • Concentration • Volume • Species (source of insulin) • Mixing 	<ul style="list-style-type: none"> • Injection site (IM vs SC) • Injection depth • Anatomic region of injection • Lipodystrophy 	<ul style="list-style-type: none"> • Temperature • Physical activity • Substances known to increase local blood flow • Massage • Hypoglycemia • Ketoacidosis • Smoking • Age • Metabolic control • Local degradation

*Changes on the injection site result in changes in local blood flow. Reprinted with permission.¹¹

culations. No comprehensive analysis of clamp data, however, has been published thus far.

A critical comparison of the different statistical methods of analysis would be worth a review by a statistician. It would be very interesting to see a comparative analysis employing different statistical approaches of data analysis generated in one study with an appropriate experimental design. However, there are probably data already generated that could be used for this purpose. Such a review might help us understand which approach is the “best” one to describe the intraindividual variability of insulin action. Unfortunately, the numbers for the CV of insulin formulations differ depending on the statistical approach used, which hampers comparison of the results of different studies. Because of differences in study design, methodologies used, and statistical analysis, the resulting data can only be compared with caution. Some form of standardization at this end would be of great value.

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VARIABILITY OF PRANDIAL INSULIN

In a study by Galloway et al,¹³ measurement of the reproducibility of the increase in serum insulin following SC injection of regular insulin in healthy subjects revealed an intraindividual CV of 63.6% for maximal serum insulin lev-

els (C_{max}) and 107.2% for time to the maximal levels (T_{max}). In a similar study,¹⁴ SC injection of 10 U of Actrapid® (Novo Nordisk A/S, Bagsvaerd, Denmark) on 4 consecutive study days in 5 healthy subjects resulted in a very low intraindividual CV for insulin absorption: 7.4% (SD, 1.3) for C_{max} and 3.4% (SD, 0.7) for $AUC_{0-300 \text{ min}}$.

Estimation of the variability of insulin absorption is also hampered by variability in both intrabatch and interbatch insulin assays, as well as potential differences between assays when determining insulin analogue concentrations, as their binding properties might differ from those of human insulin. Use of specific assays is only of limited assistance because concentrations measured by different assays also might differ.

The variability of action of regular insulin has been studied by means of the euglycemic glucose-clamp technique in only a few studies.^{2,3} Ziel et al² investigated the variability of insulin action in 8 healthy subjects after injection of 0.15 U/kg of body weight of regular insulin. This study did not investigate the total time-action profile of regular insulin, however, because the duration of glucose clamping was only 360 minutes. Further, the same insulin dose was injected on only 2 study days. The intraindividual CV was reported for only 3 pharmacokinetic summary measures (total insulin AUC, 11.2%; time to 25% of max AUC, 12.1%; time to 50% of max AUC, 10.2%) and for one pharmacodynamic summary measure (total insulin action AUC, 22.6%). The interindividual variability of the total glucose infusion, amounting to 51.3%, was considerably higher than the intraindividual variability. The authors concluded that the daily variations in insulin sensitivity have a greater impact on insulin action than does the variability of insulin absorption.

In one of our own glucose-clamp studies,³ we quantified the intraindividual variability of action of regular insulin

and the rapid-acting insulin analogue insulin aspart. Nine healthy subjects received injections of the same doses of regular insulin on 4 study days (0.2 U/kg of body weight; mean insulin dose, 14.4 U [SD, 1.6]; Actrapid® HM, U-100, Novo Nordisk A/S), and 10 subjects received injections of insulin aspart on 4 study days (same doses and concentration). The clamp duration was 600 minutes. The intraindividual CV for the majority of the pharmacodynamic summary measures was between 10% and 20%, which is relatively low and comparable to the results of Ziel et al.² The intraindividual variability of the summary measures of regular insulin did not differ from that of insulin aspart; only the late $T_{50\%}$ (time to half-maximal metabolic activity after maximal metabolic activity was reached) had a lower intraindividual variability with insulin aspart than with regular insulin. In this study, the glucose infusion rates (GIRs), which had been necessary to keep blood glucose levels constant, were continuously monitored over time. This allowed a unique presentation of the measured intraindividual variability, that is, the intraindividual CV of the

GIRs could be measured continuously over time (Figure 1).³ With both insulin preparations, the CV was 25% to 30% during the interval between 60 and 360 minutes after SC insulin injection, and metabolic activity, expressed as GIR, was >3 mg/kg per minute. Even under controlled experimental conditions, SC injection of prandial insulin displayed an intraindividual CV of insulin action of 15% to 25% and an interindividual CV of 20% to 45% (data not shown).

VARIABILITY OF INTERMEDIATE-ACTING BASAL INSULINS

Many experienced diabetologists regard a reduction in the variability of the metabolic effect of basal insulin formulations as a more clinically relevant factor than the flatness of the time-action profile achieved with different long-acting insulin analogues. Injection of basal insulin preparations was always believed to result in a greater variability of insulin action than was the injection of prandial insulin. Although this statement can be found in nearly every textbook on insulin therapy, for many years, it reflected more or less clinical experience and was not supported by data from adequately designed studies.

In the Galloway et al¹³ study, after SC injection of 0.2 U of lente insulin or neutral protamine Hagedorn (NPH) insulin into the upper arm of healthy subjects, serum insulin levels displayed an intraindividual variability in C_{max} and T_{max} of 28.3% and 33.7%, respectively, for lente insulin, and 43.6% and 68.1%, respectively, for NPH insulin. In another study that used the euglycemic glucose-clamp technique,⁴ healthy

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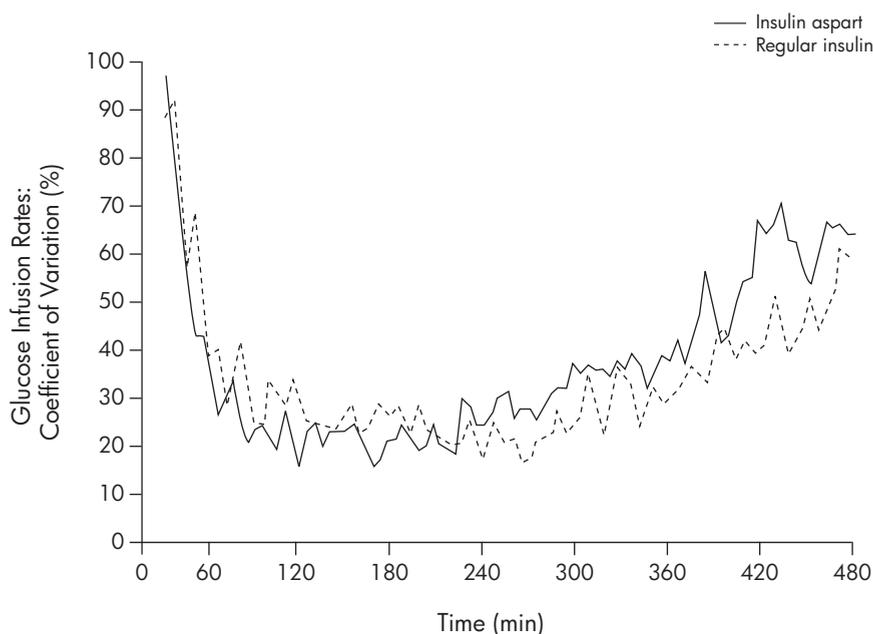


Figure 1. Mean intraindividual variability of glucose infusion rates over time after SC injection of regular insulin and insulin aspart in healthy subjects. Adapted with permission.³

subjects ($N = 8$) received injections of zinc insulin (0.4 U/kg of body weight) on 2 different study days. In this unbalanced study design, 4 different zinc insulins (1 formulated with mixed beef and pork insulin and 3 with human insulin, in ultralente or lente formulations) were injected subcutaneously into the abdomen. The intraindividual CV was 35.1% for the entire glucose amount infused, which means that the CV was not much higher with the zinc insulins than it was with regular insulin.

The long-acting insulin analogue insulin glargine is a clear but acidic preparation that contains no crystals, whereas NPH insulin is a suspension of crystals in water. Such a clear solution should distribute over a larger tissue volume after SC injection. At a neutral pH in SC tissue, insulin glargine precipitates and forms crystals of a small and uniform size. This property raises the hope that the variability of the metabolic effect might be lower with insulin glargine than with NPH insulin. In a single-dose, double-blind, randomized parallel study with 3 groups of 12 healthy subjects, the intraindividual variability of the metabolic effect induced by injection of NPH insulin, ultralente insulin, or insulin glargine was studied in 24-hour glucose clamps.⁶ On 2 study days, the subjects in each group received SC injections of 0.4 U/kg of body weight of 1 of the 3 insulin formulations into the periumbilical abdominal area. The intraindividual CVs (ANOVA) for the pharmacodynamic summary measure $AUC_{0-24\text{ h}}$ were 22% for NPH insulin, 49% for ultralente insulin, and 31% for insulin glargine. The overall variability of NPH insulin was significantly lower than that of ultralente insulin ($P < 0.05$) and tended to be lower than that of insulin glargine over the entire duration of the study.

The novel long-acting insulin analogue insulin detemir, which is also a clear preparation with a neutral pH, has a different retardation mechanism. A fatty acid attached to the insulin molecule binds to the fatty acid-binding sites of albumin; thus, nearly all absorbed insulin detemir is bound to albumin. Only a small amount, the metabolically active compound, circulates in its free form. In a glucose-clamp study, we investigated the intraindividual variability of insulin action of both insulin glargine and insulin detemir compared with that of NPH insulin in patients with type 1 diabetes mellitus (DM).¹⁵ Both insulin analogues showed less variability than did NPH insulin; however, the intraindividual variability was significantly lower with insulin detemir than with insulin glargine ($P < 0.001$). To illustrate the potential clinical relevance of reduced variability, within-subject CVs were presented as prediction intervals in this study, which by definition display 95% of the predicted values (Figure 2).¹⁵ Such prediction intervals were calculated by subtracting or adding the estimated within-subject SD multiplied by 1.96 from the least-squared mean value (LSmean): $LSmean - 1.96 \cdot SD$ or $LSmean + 1.96 \cdot SD$. An estimate of the expected frequency of hyperglycemia and hypoglycemia can be mathematically derived from the prediction intervals: patients treated with a once-daily regimen of any of the 3 insulin preparations are likely to experience a 50% reduc-

tion in the mean glucose-lowering effect of their basal insulin, which puts them at risk for pronounced hyperglycemia, ~2 times a year with insulin detemir, 57 times a year with NPH insulin, and 27 times a year with insulin glargine. Similarly, patients would experience an unusually pronounced maximum effect, potentially leading to hypoglycemia, about every second year with insulin detemir, 24 times a year with NPH insulin, and 10 times a year with insulin glargine. Therefore, under controlled experimental conditions, the intraindividual variability of the insulin action of intermediate-acting/basal insulin is not much higher than that of prandial insulin. In addition, the variability of the currently available soluble long-acting insulin analogues, insulin glargine and insulin detemir, was reduced in most but not all studies when compared with NPH insulin.

CLINICAL EXPERIENCE

Finally, what is the extent of the variability of insulin action in the daily lives of patients with diabetes, and what are its consequences? As mentioned previously, it is very likely that, in daily life, the intraindividual variability of insulin action in patients with diabetes is higher than that observed under controlled experimental conditions. Factors such as changes in the structure of SC tissue (lipodystrophy) observed in patients who inject insulin subcutaneously and repeatedly in the same skin region, insulin antibodies, changes in metabolic control, or previous hypoglycemic episodes, together with their impact on insulin sensitivity, to a large extent are eliminated under clinical experimental study conditions with healthy subjects or patients with diabetes. However, in daily life, these factors will increase the variability of insulin action, but it is not easy to estimate how the variability will increase.

Data from a clinical study¹⁶ showed that the high variability of NPH insulin in daily practice is due, at least in part, to an insufficient mixing of the suspension before drawing up the dose. The injected dose might vary considerably, depending on the manner and duration of mixing and, thus, on the amount of insulin crystals (or fluid) remaining in the vial.

MEASURES TO REDUCE VARIABILITY

Since the invention of insulin >85 years ago, a number of attempts have been made to reduce the variability of insulin absorption/insulin action, while also modifying other pharmacologic properties of a given insulin formulation. For example, investigators hypothesized that alterations in the insulin molecule and/or in the insulin formulation could lead to reduced variability. It was hoped that the invention of rapid-acting and long-acting insulin analogues would decrease variability. However, the studies here discussed have demonstrated practically no reduced variability in the induced metabolic effect with rapid-acting insulin analogues, while significant improvements with long-acting insulin analogues have been observed.

Other routes of insulin administration might offer an interesting opportunity to reduce the intraindividual vari-

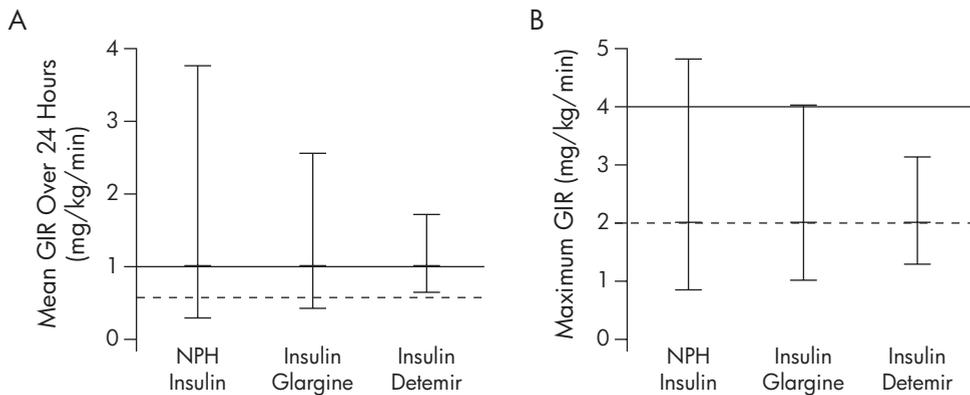


Figure 2. Within-subject variability of neutral protamine Hagedorn (NPH) insulin, insulin glargine, and insulin detemir is shown by the width of a prediction interval containing 95% of the predicted values. The prediction intervals illustrating day-to-day variability in the pharmacodynamic response are exemplified for a subject with the same mean response with any given treatment (ie, NPH insulin, insulin glargine, or insulin detemir). A subject with a mean glucose infusion rate (GIR) over 24 hours of 1 mg/kg per minute has a probability to experience an effect of less than half the usual effect (ie, <0.5 mg/kg per minute) of 16% with NPH insulin, 7% with insulin glargine, and 0.5% with insulin detemir (A). Similarly, for a subject with a maximum effect of 2 mg/kg per minute, the probability of experiencing a maximum effect of more than twice the usual level (ie, >4 mg/kg per minute) will be 6% with NPH insulin, 3% with insulin glargine, and 0.1% with insulin detemir (B). Note: A linear scale has been used in this figure to improve readability of values; therefore, the prediction intervals are not distributed symmetrically around the mean. Adapted with permission.¹⁵

ability of the metabolic effect because they circumvent the variability of insulin absorption from the insulin depot in SC tissue. The only other route of administration currently available is inhalation. One might assume that with a single dose of inhaled insulin (eg, 50 U), a variability of 30% might present a serious safety problem due to the low therapeutic index of insulin. This would be true if the effective dose actually varied between 35 and 65 U. With a relative biopotency of 20% with inhaled insulin, the effective dose would vary between 7 and 13 U. However, a relative biopotency of 20% is a high value—the relative biopotency of most formulations is between 10% and 15%. Biopotency is the metabolic effect induced by inhalation of insulin compared with that induced by SC injection, with dose correction.

Since the invention of insulin >85 years ago, a number of attempts have been made to reduce the variability of insulin absorption/insulin action, while also modifying other pharmacologic properties of a given insulin formulation.

In one of our own glucose-clamp studies among healthy subjects, an identical insulin dose was inhaled on 3 study days.⁷ The intraindividual variability of a number of pharmacokinetic and pharmacodynamic summary measures

after insulin inhalation was comparable to that of subcutaneously injected regular insulin. In another glucose-clamp study, Brunner et al⁸ examined the dose-response relationship with 4 doses of inhaled insulin (0.3, 0.6, 1.2, and 1.8 U/kg) in patients with type 1 DM. The intraindividual variability (based on doses of 0.6 and 1.2 U/kg) was reported for only 2 parameters (AUC–insulin_{0–10h} and AUC–GIR_{0–10h}). The CV for AUC–GIR_{0–10h} in patients with type 1 DM was more than twice that in healthy subjects (34% vs 16%, respectively). The intraindividual variability of insulin action after inhalation of 100 IU of insulin (Technosphere™ Insulin System, Mannkind Corporation, Valencia, California) on 3 study days observed in 12 patients with type 2 DM was also within the range of that observed with subcutaneously administered regular insulin in healthy subjects.⁹ Another glucose-clamp study among 15 nonsmoking patients with type 2 DM who inhaled 240 U of insulin (Aerodose® inhaler, AeroGen, Inc., Sunnyvale, California) on 2 study days revealed no significant differences in the CVs of a number of pharmacokinetic and pharmacodynamic summary measures compared with 24 U of subcutaneously administered regular insulin on 2 other study days.¹⁰

The good reproducibility with pulmonary application of insulin might be explained by the fact that the blood flow through the absorptive epithelial surface of the lung is more homogeneous than it is in the SC compartment, where variable amounts of fat and connective tissue might be served by different degrees of capillary perfusion following an injection.¹⁷

These studies show that the variability of the metabolic effect observed after inhalation of insulin (15%–30%) is comparable to that seen after SC administration of prandial insulin. Therefore, this novel application form does not represent a measure to reduce the variability of the metabolic effect, but neither should it induce a higher risk with respect to the variability of action. It would be interesting to investigate in head-to-head comparisons whether the variability of inhaled insulin formulations differs.

The variability of the metabolic effect observed after inhalation of insulin (15%–30%) is comparable to that seen after SC administration of prandial insulin.

CONCLUSIONS

The intraindividual variability of insulin action after SC administration can be assumed to be 15% to 25% with prandial insulin and 25% to 35% with basal insulin. Further, it seems likely that the variability of insulin action in patients with diabetes under conditions of daily life is higher than that under controlled experimental conditions. How much higher, however, we cannot tell.

There are no appropriate studies investigating the variability of insulin action after SC administration in different groups of patients with diabetes in a head-to-head com-

Our knowledge about the extent of insulin variability, its reasons, and its quantitative impacts, as well as about possible ways to reduce this variability, is still limited. More research about this clinically highly relevant topic should be undertaken.

parison (ie, within 1 study). Not only would such a comparison between patients with type 1 DM and type 2 DM be of interest, but a comparison of various patient groups with type 2 DM (eg, slim vs obese patients) might also show differences. Treatment with other antidiabetic drugs in addition to insulin might also have an impact on variability, probably also other drugs that have an effect on SC blood flow.

Findings from the first canine insulin experiments performed by its inventors in 1921 to 1922 demonstrated that injection of identical insulin doses (what were believed to be identical doses at this stage of insulin development) resulted in differences in the metabolic effect induced. After more than 85 years of insulin research, our knowledge about the extent of this variability, its reasons, and its quantitative impacts, as well as about possible ways to reduce this variability, is still limited. More research about this clinically highly relevant topic should be undertaken. To date, no means have been found that could lead to a clinically relevant reduction in the variable metabolic effect.

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