

Lower Within-Subject Variability of Insulin Detemir in Comparison to NPH Insulin and Insulin Glargine in People With Type 1 Diabetes

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The aim of this randomized double-blind study was to compare the within-subject variability of the glucose-lowering effect of a novel insulin analog, insulin detemir, with that of insulin glargine and NPH insulin in people with type 1 diabetes. Fifty-four subjects (32 males and 22 females, age 38 ± 10 years [mean \pm SD], BMI 24 ± 2 kg/m², HbA_{1c} $7.5 \pm 1.2\%$, diabetes duration 18 ± 9 years) participated in this parallel group comparison. Each subject received four single subcutaneous doses of 0.4 units/kg of either insulin detemir ($n = 18$), insulin glargine ($n = 16$), or human NPH insulin ($n = 17$) under euglycemic glucose clamp conditions (target blood glucose concentration 5.5 mmol/l) on four identical study days. The pharmacodynamic (glucose infusion rates [GIRs]) and pharmacokinetic (serum concentrations of insulin detemir, human insulin, and insulin glargine) properties of the basal insulin preparations were recorded for 24 h postdosing. Insulin detemir was associated with significantly less within-subject variability than both NPH insulin and insulin glargine, as assessed by the coefficient of variation (CV) for the pharmacodynamic end points studied [GIR-AUC_(0-12 h) 27% (detemir) vs. 59% (NPH) vs. 46% (glargine); GIR-AUC_(0-24 h) 27 vs. 68 vs. 48%; GIR_{max} 23 vs. 46 vs. 36%; $P < 0.001$ for all comparisons]. Insulin detemir also provided less within-subject variability in the pharmacokinetic end points: maximal concentration (C_{max}) 18 vs. 24 vs. 34%; INS-AUC_(0-∞) 14 vs. 28 vs. 33%. The results suggest that insulin detemir has a significantly more predictable glucose-lowering effect than both NPH insulin and insulin glargine. *Diabetes* 53:1614-1620, 2004

Daily clinical experience indicates that subcutaneous administration of insulin often does not result in a reproducible metabolic effect even when injected at the same dose under comparable conditions. Nonetheless, only few studies have as-

sessed the variability of insulin absorption after subcutaneous administration (1-7), and even fewer have assessed the variability in the glucose-lowering effect of insulin. Thus, even though variability of the glucose-lowering effect is regarded as a major obstacle to achieving optimal metabolic control (8-10), our knowledge of the variability of insulin preparations is surprisingly scarce (11,12).

This is particularly true for basal insulin preparations. The few studies available report coefficients of variation (CVs) for within- and between-subject variability in the pharmacodynamic action of long-acting zinc insulin preparations to be between 35 and 55% (9) and even greater for NPH insulin (13). Compared with these findings, the variability (CV) of short-acting insulin preparations, which are reported in the range of "only" 20-30% (10,11), are less of a concern. The development of the new long-acting insulin analogs such as insulin detemir and insulin glargine has raised the hope of concurrent lower within-subject variability. However, insulin glargine does not appear to provide any improvement in the within-subject variability compared with NPH insulin (8).

The aim of this study was to compare the within-subject variability in the glucose-lowering effect of the novel long-acting insulin analog insulin detemir with that of NPH insulin and insulin glargine. Insulin detemir [Lys^{B29}(N^ε-tetradeconoyl) des(B30) human insulin] is the first of a new class of long-acting soluble insulin analogs. Its prolonged duration of action is attributable to a combination of increased self-association (hexamer stabilization 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). Insulin detemir is highly albumin bound in the interstitial fluid and in plasma (14) and has been shown to elicit a protracted metabolic action, with a slow onset of action and a less pronounced peak of action compared with that observed for NPH insulin (15,16).

Absorption of insulin detemir, which is presented as a clear neutral solution (14), is dependent on neither appropriate resuspension before injection and dissolution of crystals in the subcutaneous tissue, as is the case for NPH insulin, nor on formation and dissolution of microprecipitates, as is the case for insulin glargine. Thus, insulin detemir should provide a more constant and reliable basal insulin supply than other basal insulin preparations. The aim of this study was to investigate whether the glucose-

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AUC, area under the curve; ELISA, enzyme-linked immunosorbent assay; GIR, glucose infusion rate; GIR_{max}, maximum GIR.

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lowering effect of insulin detemir is more predictable than that of the two most often used basal insulin preparations, i.e., NPH insulin and insulin glargine.

RESEARCH DESIGN AND METHODS

This was a single-center, parallel group, double-blind trial designed to investigate the within-subject variability in pharmacodynamic and pharmacokinetic end points for insulin detemir, NPH insulin, and insulin glargine in subjects with type 1 diabetes. The study protocol was reviewed and approved by the local ethics committee and was performed according to GCP/ICH guidelines and the Declaration of Helsinki. After giving signed informed consent, 54 eligible subjects with type 1 diabetes (32 males and 22 females, age 38 ± 10 years [means \pm SD], BMI 24 ± 2 kg/m², HbA_{1c} $7.5 \pm 1.2\%$, diabetes duration 18 ± 9 years, C-peptide ≤ 0.5 ng/ml) were randomly assigned to four single doses of one of the three basal insulin preparations.

The subjects attended the study site in the morning after an overnight fast and were connected to a Biostator (glucose controlled insulin infusion system [GCIS]; MTB Medizintechnik, Ulm, Germany) at least 4 h before trial drug administration. Throughout the clamp procedure the subjects remained fasting (apart from water) and in a supine position. Basal insulin could be taken 12–24 h before trial drug administration, whereas no insulin could be taken in the morning of the dosing day.

Subjects received a variable intravenous infusion of human regular insulin in order to maintain a target blood glucose level of 100 mg/dl (5.5 mmol/l). The intravenous insulin infusion rate was lowered to a level where the blood glucose remained stable, and no glucose infusion was required 1 h before trial drug administration to avoid confounding the glucose-lowering effect of the trial drugs. On the first dosing day, the subjects were randomized to receive a single dose of 0.4 units/kg of either insulin detemir (100 units/ml; Novo Nordisk, Bagsvaerd, Denmark), NPH insulin (Insulatard, 100 IU/ml; Novo Nordisk), or insulin glargine (Lantus, 100 IU/ml; Aventis Pharma, Frankfurt, Germany) by subcutaneous injection into a lifted skinfold in the thigh. Each subject completing the trial underwent identical dosing-day procedures and received the same insulin preparation and dose on all four dosing days. NPH insulin was thoroughly resuspended before administration. All injections were performed with a syringe by a person otherwise not involved in the study to keep the double-blind character of this study. The time interval between the study days was 5–21 days, during which the subjects reverted to their usual insulin treatment regimen.

Due to the glucose-lowering effect of the injected insulin, glucose had to be infused intravenously at some time point after dosing to prevent a decline in blood glucose. When the glucose infusion rate (GIR) increased >1 mg \cdot kg⁻¹ \cdot min⁻¹ for 10 min, the initial intravenous human insulin infusion was stopped. There were no relevant differences between treatments regarding the amount of insulin infused intravenously after trial drug administration (0.01 ± 0.012 units/kg [insulin detemir], 0.01 ± 0.010 IU/kg [NPH insulin], 0.01 ± 0.007 IU/kg [insulin glargine]). The GIR necessary to keep blood glucose levels constant was recorded every minute for 24 h postdosing. The euglycemic glucose clamp procedure was stopped earlier if blood glucose increased to >11.1 mmol/l (200 mg/dl) without any glucose having been administered for at least 30 min (glucose infusion was stopped by the Biostator when blood glucose concentrations exceeded the clamp level of 5.5 mmol/l for several minutes).

Blood samples for blood glucose and pharmacokinetic analyses (serum levels of insulin detemir, human insulin, or insulin glargine, depending on the study medication applied) were drawn at the following time points: 0 (immediately before the subcutaneous injection of the trial drug), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, and 28 h postdosing.

Serum insulin detemir concentrations were measured using a specific enzyme-linked immunosorbent assay (ELISA) method (15), serum human insulin was measured using a commercially available insulin ELISA, and serum insulin glargine concentrations were measured using a combination of two commercially available ELISA kits (MercoDia Iso-insulin ELISA method and Dako ELISA). Calibrators, however, were prepared to obtain good correlation between the two assays. Using mass spectrometry, it was found that, within 1 h at 37°C, insulin glargine in human serum is degraded into Stabilin (Gly A21 human insulin). The exact insulin glargine concentration was calculated from the results of the Dako insulin ELISA (detecting only human insulin) and from the results obtained with the MercoDia Iso-insulin ELISA (detecting human insulin and insulin glargine). The lower limit of quantification was 25 pmol/l for insulin detemir, 11 pmol/l for human insulin, and 21 pmol/l for insulin glargine.

Statistical methods. All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC). The GIR profiles were smoothed using locally weighted regression (using the SAS procedure LOESS) to allow for the determination of the pharmacodynamic end points GIR-AUC_(0–12 h), GIR-

TABLE 1
Demographic characteristics of the three treatment groups

	Insulin detemir	NPH insulin	Insulin glargine
Male (%)	72	61	44
Age (years)	38 ± 10	41 ± 10	34 ± 8
BMI (kg/m ²)	24.2 ± 2.2	24.5 ± 2.9	24.5 ± 2.0
Diabetes duration (years)	18 ± 7	19 ± 9	18 ± 9
HbA _{1c} (%)	7.5 ± 1.1	7.4 ± 1.3	7.4 ± 1.2

Data are means \pm SD.

AUC_(0–24 h), GIR-AUC_(2–24 h) (areas under the glucose infusion rate profiles in the time intervals from 0–12, 0–24, and 2–24 h, respectively), GIR_{max} (maximum glucose infusion rate), and t_{GIRmax} (time to GIR_{max}).

Pharmacodynamic end points were compared between treatments after log transformation using a mixed ANOVA model with trial drug and period included as fixed effects, subjects included as a random effect with variance depending on the treatment group, and an error term with a variance depending on the treatment group.

Pairwise comparisons of within-subject variances (expressed as CV and calculated as the square root of the within-subject variance) were made between insulin detemir and NPH insulin and between insulin detemir and insulin glargine. Ongoing metabolic effect of a trial drug beyond the clamp duration was defined as a glucose infusion rate >0.2 mg \cdot kg⁻¹ \cdot min⁻¹ in the time interval from 23 to 24 h postdosing.

The pharmacokinetic end points INS-AUC_(0–12 h), INS-AUC_(0–∞), and maximum concentration (C_{max}) were analyzed using an ANOVA mixed model separately for each insulin preparation.

Finally, 95% prediction intervals were calculated by subtracting and adding the estimated within-subject SD multiplied by 1.96 from the least-squared mean value (least-squared mean value $- 1.96 \times$ SD; least-squared mean value $+ 1.96 \times$ SD).

RESULTS

There were no clinically relevant differences in demographic characteristics between subjects in the three treatment groups (Table 1). A total of 51 subjects completed the trial (18 on insulin detemir, 17 on NPH insulin, and 16 on insulin glargine). One subject randomized to insulin glargine withdrew consent for private reasons, one subject randomized to insulin glargine was withdrawn due to technical difficulties with the glucose clamp procedure (bad vein condition), and one subject randomized to NPH insulin was withdrawn due to an adverse event (skin burn). **Pharmacodynamics.** The within-subject variability for GIR-AUC_(0–12 h) was significantly lower for insulin detemir (CV 27%) compared with NPH insulin (59%) and insulin glargine (46%) ($P < 0.001$ for both comparisons). Similarly, within-subject variability over 24 h [GIR-AUC_(0–24 h)] was lower for insulin detemir compared with both NPH insulin and insulin glargine ($P < 0.001$ for both comparisons). The differences in variability were even more pronounced when the first 2 h of the glucose clamp procedure were excluded from the assessment [GIR-AUC_(2–24 h)]. Although t_{GIRmax} was ~ 500 min for all three insulin preparations, the within-subject variability of the level of GIR_{max} was significantly lower for insulin detemir than for NPH insulin and insulin glargine (Table 2).

Mean values for GIR-AUC and for GIR_{max} were lower for insulin glargine than for either of the other two insulin preparations (Table 2). However, due to the lower within-subject variability of insulin detemir, the highest expected GIR_{max} values for individual subjects are lower with insulin detemir. GIR_{max} for an individual subject will be >2 SDs above the mean in 2.5% of all dose administrations,

TABLE 2
Pharmacodynamics and pharmacokinetics of the three treatment groups

	Means \pm SD			CVs (%)		
	Insulin detemir	NPH insulin	Insulin glargine	Insulin detemir	NPH insulin	Insulin glargine
Pharmacodynamics						
GIR-AUC _(0-12 h) (mg/kg)	1,130 \pm 312	1,280 \pm 559	886 \pm 325	27	59*	46*
GIR-AUC _(0-24 h) (mg/kg)	1,703 \pm 490	1,923 \pm 765	1,474 \pm 498	27	68*	48*
GIR-AUC _(2-24 h) (mg/kg)	1,608 \pm 459	1,831 \pm 744	1,377 \pm 482	27	77*	66*
GIR _{max} (mg \cdot kg ⁻¹ \cdot min ⁻¹)	2.3 \pm 0.5	2.7 \pm 1.1	1.8 \pm 0.6	23	46*	36*
Pharmacokinetics						
INS-AUC _(0-12 h) (nmol \cdot min ⁻¹ \cdot l ⁻¹)	1,295 \pm 201	75 \pm 20	46 \pm 16	15	26	34
INS-AUC _(0-∞) (nmol \cdot min ⁻¹ \cdot l ⁻¹)	2,355 \pm 323	162 \pm 48	128 \pm 42	14	28	33
C _{max} (pmol/l)	2,865 \pm 626	147 \pm 40	99 \pm 33	18	24	34

* $P < 0.001$ vs. insulin detemir.

and hence subjects receiving insulin detemir reach GIR_{max} >3.3 mg \cdot kg⁻¹ \cdot min⁻¹ in 2.5% of all dose administrations, subjects receiving NPH insulin reach GIR_{max} >5.8 mg \cdot kg⁻¹ \cdot min⁻¹, and subjects receiving insulin glargine reach GIR_{max} >3.4 mg \cdot kg⁻¹ \cdot min⁻¹.

Metabolic activity was ongoing after 24 h in 17 of 72 (24%) clamps performed with insulin detemir (7 different subjects), whereas NPH insulin showed ongoing activity in 10 of 69 (14%) clamps (5 different subjects) and insulin glargine in 25 of 64 (39%) clamps (14 different subjects).

The differences in within-subject variability between the insulin preparations are readily illustrated in the individual GIR profiles for the first nine subjects treated in each treatment group (Fig. 1). The GIR profiles for insulin detemir were generally more consistent over the four dosing days compared with those for NPH insulin and insulin glargine.

Pharmacokinetics. Comparisons between serum insulin concentration levels are not meaningful since the three insulin preparations are different chemical entities with different modes of protraction administered in different molar doses. Moreover, within-subject variability of pharmacokinetic end points should be interpreted with caution as the precision of the assays used to assess serum insulin concentrations with each insulin preparation differs and will therefore contribute slightly to the within-subject variability estimated. Nevertheless, within-subject variability for the pharmacokinetic end points, INS-AUC_(0-12 h), INS-AUC_(0-∞), and C_{max} were generally lower with insulin detemir than with NPH insulin and insulin glargine, which is consistent with the pharmacodynamic results (Table 2).

Safety. Subcutaneous administration was generally well tolerated for all three basal insulin preparations. Only three adverse events were regarded as being possibly and/or probably related to trial drug: one subject reported two events of swelling at the injection site (insulin detemir), and one subject reported one event of vomiting (NPH insulin). There were no clinically relevant safety findings in other safety parameters, including laboratory variables of hematology and biochemistry.

DISCUSSION

This is the first trial designed to systematically compare the within-subject variability of the pharmacodynamic and pharmacokinetic properties of insulin detemir with the two most commonly used basal insulin preparations, NPH

insulin and insulin glargine. The results demonstrate that the newly developed long-acting analog, insulin detemir, has a more predictable glucose-lowering effect with a significantly lower within-subject variability than either of the other insulin preparations. The lower within-subject variability observed for the pharmacodynamic end points was consistent with lower within-subject variability for the pharmacokinetic end points.

The high within-subject variability in the pharmacodynamic action of available basal insulin preparations has been reported previously as CVs (for example, CVs for NPH insulin have ranged from 18 to 68% in different studies) (12). The wide range of CVs reported in different studies is probably due to the variety of methods used (radioactively labeled insulin [3,5], pharmacokinetic or pharmacodynamic measurements), differences regarding the number of replicate measurements (two to six [8,12,17,18]), and the injection site (thigh [13,18], upper arm [13], or abdomen [13]). The method to calculate variability also differs between studies. In this study, within-subject CV was calculated as the square root of the within-subject variance using logarithmically transformed end points. Calculating CVs in this way provides an unbiased estimate of the true within-subject variability, whereas the method that is usually used (CV = SD/mean) may result in an underestimation of the true within-subject variability (19,20). But even when using the usual approach based on the non-log transformed data, within-subject variation is still lower with insulin detemir than with NPH insulin and insulin glargine (Novo Nordisk, data on file).

The high variability for NPH insulin observed here and reported in previous trials (13) may have been expected because NPH insulin is a suspension of crystals, and dissolution of crystals in the subcutaneous tissue is one of the sources of variation. Furthermore, it has been shown that the need to thoroughly resuspend the NPH insulin before injection is often disregarded by patients with diabetes (21), which clearly contributes to the high variability of NPH insulin in clinical practice (22). In this study, appropriate resuspension of NPH insulin was ensured by experienced clinical staff.

Considering that both long-acting insulin analogs, insulin detemir and insulin glargine, are presented as clear solutions, one might assume that both analogs would be associated with lower variability compared with NPH insulin. However, in a previous trial, no difference could be

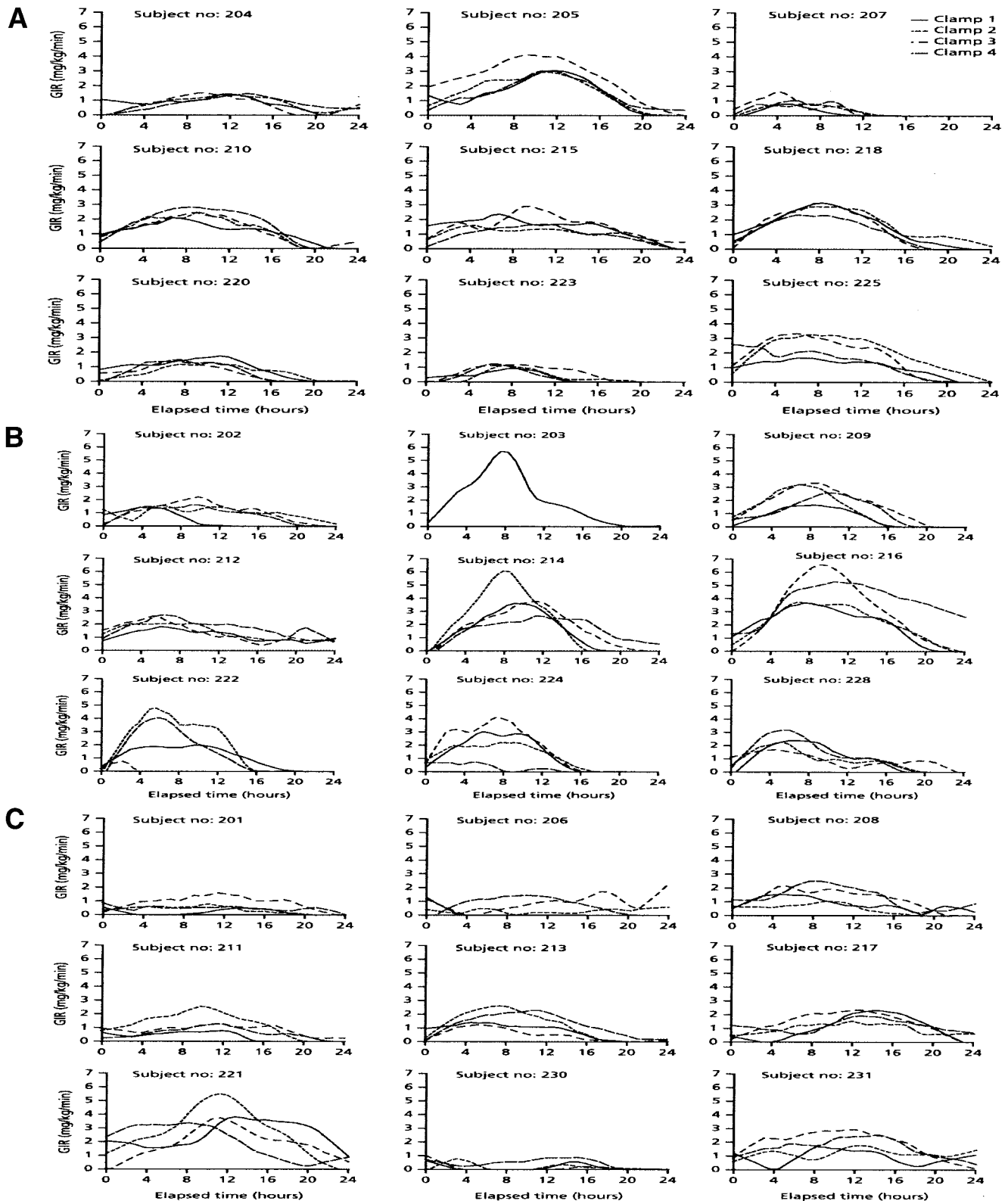


FIG. 1. Individual time-action profiles (glucose infusion rates over time) of the first nine patients randomized to insulin detemir (A), NPH insulin (B), or insulin glargine (C). The four clamps in one subject are summarized in one plot. A low within-subject variability is indicated by the four lines in one plot being close to each other (e.g., subject no. 204), whereas major deviations between the time-action profiles in one subject (e.g., subject no. 224) shows a high within-subject variability.

demonstrated between insulin glargine and NPH insulin (8). In contrast, the within-subject variability was substantially lower with insulin detemir than with both NPH

insulin and insulin glargine in this trial. The observed difference in variability between the two insulin analogs may be related to the different modes of protraction.

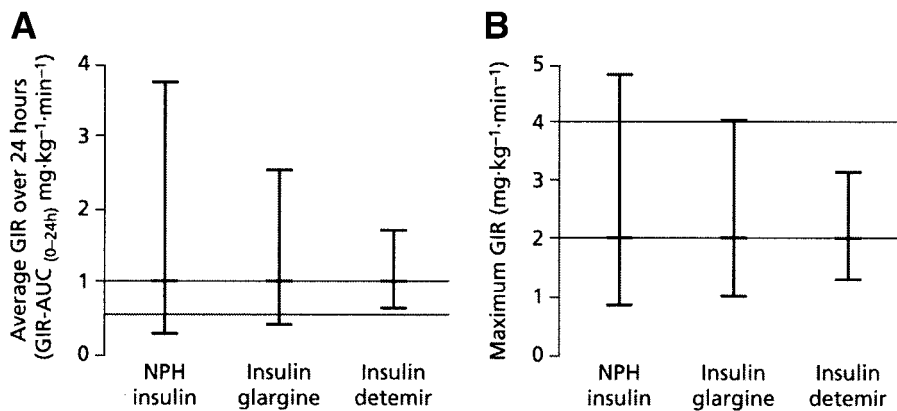


FIG. 2. Within-subject variability of insulin detemir, NPH insulin, and insulin glargine are graphically shown by the width of a prediction interval containing 95% of the predicted values. The prediction intervals illustrating day-to-day variability in the pharmacodynamic response are exemplified for a subject with the same mean response with any given treatment (insulin detemir, NPH insulin, or insulin glargine). **A:** A subject with a mean GIR over 24 h of $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ has a probability to experience an effect of less than half the usual effect (i.e., $<0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) of 0.5% using insulin detemir, 16% with NPH insulin, and 7% with insulin glargine. **B:** Similarly, for a subject with a maximum effect of $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, the probability of experiencing a maximum effect of more than twice the usual level (i.e., $>4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) will be 0.1% if the subject uses insulin detemir, 6% with NPH insulin, and 3% with insulin glargine. Note: a linear scale has been used in this figure to improve readability of values, and therefore the prediction intervals are not distributed symmetrically around the mean.

Insulin detemir stays in solution in the subcutaneous depot, in the circulation, and in the target tissues until interacting with the insulin receptor. Insulin glargine on the other hand forms microprecipitates after subcutaneous injection (23), which must redissolve before absorption can take place. Precipitation and redissolution are processes inherently associated with a substantial variability.

Due to the higher molar dose and binding to albumin, insulin detemir (1 unit = 24 nmol/l) is associated with higher serum concentrations than NPH insulin (1 IU = 6 nmol/l) and insulin glargine (1 IU = 6 nmol/l). Thus, for insulin detemir, in addition to the subcutaneous depot at the injection site, there are other depots related to albumin binding in plasma and interstitial fluid. The reversible albumin binding of insulin detemir is likely to contribute to the lower pharmacokinetic and pharmacodynamic variability by acting as a buffer against rapid or irregular changes for instance in insulin absorption. It is therefore not surprising that within-subject variability of the pharmacokinetics of insulin detemir were reported to be lower than those of NPH in an earlier trial (17).

The pharmacodynamic results observed in this study are in agreement with previously reported data for all three insulin preparations studied (15,24–26). However, it should be noted that considerable variation in the individual profiles was observed between subjects (Fig. 1). It is striking that many subjects showed a characteristic response for any of the insulin preparations studied. The differences in the shape of the GIR profiles are rather small between the glucose clamps of one individual, but are huge between subjects receiving the same treatment. This finding has also been observed in other studies reporting individual data (8,11) and indicates a specific individual pattern of insulin absorption and action.

Potential limitations of the study design have to be taken into account when interpreting the results. One potential limitation is the fact that human insulin was infused during the initiation of the clamp procedure in order to maintain the clamp target before onset of the injected insulin. Although the actual level of infused insulin was small with all three insulin preparations ($\sim 0.1 \text{ IU/kg}$), exclusion of GIR data from the first 2 h after administration [$\text{GIR-AUC}_{(2-24 \text{ h})}$] had a marked effect on

the estimates for within-subject variability compared with those for the entire GIR profile [$\text{GIR-AUC}_{(0-24 \text{ h})}$], especially for NPH insulin and insulin glargine. While the CV for insulin detemir remained unchanged, the CVs for both NPH insulin and insulin glargine increased substantially (Table 2). One explanation for this observation could be that the within-subject CV for the effect over the first 2 h after injection is underestimated for NPH insulin and insulin glargine, due to a possible buffering effect related to the contribution of human insulin infusion (which was continued until GIR increased to $>1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 10 min). Alternatively, it may be that the within-subject variability of the effects in the early phase (0–2 h) for NPH insulin and insulin glargine are lower than in the later phase (2–24 h), whereas insulin detemir is equally predictable during both phases.

Another potential limitation of the study design is that a fixed single dose of 0.4 units/kg was given. Although it cannot be ruled out that the CV might differ with dose level, the comparisons of within-subject variability are based on the ratio of CVs and are therefore unlikely to be affected by dose levels. Moreover, the dose was chosen as close as possible to the mean dose for both insulin detemir (0.37 units/kg) and NPH insulin (0.39 IU/kg) in the phase III program of insulin detemir (Novo Nordisk, data on file) and the median daily dose for insulin glargine in clinical trials (reported to be in a range of 17–33 IU in type 1 diabetic patients [27], which should correspond to a dose close to 0.4 units/kg). It also seems unlikely that the single-dose condition affects the conclusions in this trial, since insulin detemir has been shown to reach steady-state already after two twice-daily injections (28) and no significant accumulation was found for insulin glargine in an earlier pharmacokinetic trial (29). These data indicate that there is no substantial difference in the overall pharmacodynamic effect between steady-state and single-dose conditions for the insulin preparations studied. Thus, the differences in variability between the insulin preparations are probably due to the different modes of protraction.

As could be expected, ongoing metabolic activity after 24 h was correlated within subjects. This was more pronounced for insulin detemir—17 clamps with ongoing metabolic activity occurred in 7 patients compared with 10

clamps in 5 patients for NPH insulin and 25 clamps in 14 patients on insulin glargine. This suggests that the duration of action of insulin detemir and insulin glargine may be sufficient for once-daily use in a substantial number of patients. The duration of action of insulin detemir has been reported to be longer with higher doses in both single-dose and steady-state conditions (16,28).

To illustrate the potential clinical relevance of reduced variability, within-subject CVs are presented as prediction intervals, which by definition display 95% of the predicted values (Fig. 2). An estimate of the expected frequency of hyper- and hypoglycemia can be mathematically derived from the prediction intervals: a patient treated in a once-daily regimen with any of the three insulin preparations is likely to experience a 50% lower-than-usual average glucose-lowering effect of their basal insulin (putting them at risk of pronounced hyperglycemia) about twice a year with insulin detemir, 57 times a year with NPH insulin, and 27 times a year with insulin glargine. Similarly, the patient 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. Although caution should be taken when making such extrapolations from experimental situations to clinical practice, it is worth noting that the predicted lower risk of hypoglycemia was in agreement with the results of treatment trials, which have consistently shown a reduction in the incidence of hypoglycemic episodes and a lower variation in fasting blood glucose compared with NPH insulin (30–34). Taken together, these results indicate that the observed lower within-subject variability of insulin detemir may prove to be important for patients on insulin therapy, enabling improved metabolic control with less day-to-day fluctuations in blood glucose.

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