Comparison of Pharmacokinetics and Dynamics of the Long-Acting Insulin Analogs Glargine and Detemir at Steady State in Type 1 Diabetes

A double-blind, randomized, crossover study

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OBJECTIVE — To compare pharmacokinetics and pharmacodynamics of insulin analogs glargine and detemir, 24 subjects with type 1 diabetes (aged 38 ± 10 years, BMI 22.4 ± 1.6 kg/m^2, and A1C 7.2 ± 0.7%) were studied after a 2-week treatment with either glargine or detemir once daily (randomized, double-blind, crossover study).

RESEARCH DESIGN AND METHODS — Plasma glucose was clamped at 100 mg/dl for 24 h after subcutaneous injection of 0.35 unit/kg. The primary end point was end of action (time at which plasma glucose was >150 mg/dl).

RESULTS — With glargine, plasma glucose remained at 103 ± 3.6 mg/dl up to 24 h, and all subjects completed the study. Plasma glucose increased progressively after 16 h with detemir, and only eight subjects (33%) completed the study with plasma glucose <180 mg/dl. Glucose infusion rate (GIR) was similar with detemir and glargine for 12 h, after which it decreased more rapidly with detemir ($P < 0.001$). Estimated total insulin activity (GIR area under the curve $[AUC]_{0-\text{end of GIR}}$) was 1,412 ± 662 and 915 ± 225 mg/kg (glargine vs. detemir, $P < 0.05$), with median time of end of action at 24 and 17.5 h (glargine vs. detemir, $P < 0.001$). The antilipolytic action of detemir was lower than that of glargine (AUC free fatty $acids_{0-24\ h}$ 11 ± 1.7 vs. 8 ± 2.8 mmol/l, respectively, $P < 0.001$).

CONCLUSIONS — Detemir has effects similar to those of glargine during the initial 12 h after administration, but effects are lower during 12–24 h.

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Abbreviations: AUC, area under the curve; FFA, free fatty acid; GIR, glucose infusion rate; IIR, intravenous insulin infusion rate; IV, intravenous; SC, subcutaneous.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The soluble long-acting insulin analogs glargine and detemir exhibit more physiological pharmacokinetic and pharmacodynamic characteristics than NPH, i.e., a flatter action profile with a longer duration of action (1–3), particularly after several days of use (4), in addition to lower within-subject variability (3) and lower fluctuations (5). These pharmacokinetic and pharmacodynamic advantages translate into a reduced risk of nocturnal hypoglycemia in type 1 diabetes compared with NPH (6–9).

Several clinical experimental studies have examined glargine or detemir versus NPH in type 1 diabetes, but no study has been conducted to compare these insulin analogs directly in the same subjects at steady state to establish relative pharmacokinetics and pharmacodynamics after a therapeutic dose. However, glargine and detemir are different chemical and structural entities (1). Therefore, it is conceivable that in a head-to-head comparison, the two analogs might exhibit different pharmacokinetics and pharmacodynamics. Thus, the aim of the present study was to establish the pharmacokinetics and pharmacodynamics of the long-acting insulin analogs glargine and detemir in type 1 diabetes with "intrasubject" comparison at steady state, after injection of a dose of insulin similar to that used in the clinical setting in most of our type 1 diabetic patients.

RESEARCH DESIGN AND METHODS

— The study was approved by the local ethics committee and conducted according to the Declaration of Helsinki and Good Clinical Practice requirements. After giving informed, written consent, 24 type 1 diabetic subjects (14 men, aged 38 ± 10 years, BMI 22.4 ± 1.6 kg/m^2, A1C 7.2 ± 0.7%, diabetes duration 18 ± 7 years, and fasting plasma C-peptide <0.02 nmol/l), naïve to either glargine or detemir, were recruited. All subjects had been receiving intensified in-

sulin therapy with multiple daily injections of NPH as the basal insulin and rapid-acting insulin analogs at meals, as reported previously (10), for at least 3 years. Patients were free of any detectable microangiopathic complication and tested negative at the screening for autonomic neuropathy, as determined by a standard battery of cardiovascular tests (11).

The study was a randomized, single-dose, double-blind, two-way, crossover study using the euglycemic glucose clamp technique (12). After a 4-week run-in period, during which the previous insulin therapy regimen was continued (10), NPH insulin was withdrawn and subjects were randomly assigned to a once-daily dose of either glargine ($n = 12$ subjects) or detemir ($n = 12$ subjects) given by syringes at 7:00 P.M., for a period of 2 weeks. Rapid-acting insulin analogs (either lispro or aspart) were continued before each meal. The dose of basal insulin was titrated to reach a fasting plasma glucose concentration of 100 mg/dl, while avoiding nocturnal hypoglycemia (plasma glucose <72 mg/dl) (10). The dose of rapid-acting analog was titrated to keep the 2-h postprandial plasma glucose concentration <145 but >72 mg/dl. For the entire duration of the study, all subjects monitored blood glucose by means of a reflectometer (LifeScan One Touch Ultra; Johnson & Johnson, Milpitas, CA).

After a 14-day treatment, all subjects underwent an euglycemic clamp for 24 h, after subcutaneous (SC) injection of the basal insulin they were receiving, either glargine (0.35 unit/kg) or detemir (0.35 unit/kg) (2). This was followed by a washout period of 2 weeks, during which they resumed the insulin regimen of the run-in period. The subjects were then crossed over to treatment with the other basal insulin and at the end of the last 2 weeks were studied again with the euglycemic clamp technique for 24 h.

Euglycemic clamp

The procedure described previously for euglycemic clamp (2) was used, but the target plasma glucose was 100 mg/dl and time 0 min of the study was 7:00 P.M. (SC injection of the basal insulin analog). The last SC injection of the rapid-acting insulin analog was at 12:00 noon (before a standardized meal: 688 kcal, 54% carbohydrate, 30% protein, and 16% lipids), and an intravenous (IV) feedback insulin infusion was initiated at 2:30 P.M. to maintain plasma glucose at 118–135 mg/dl between 3:00 and 5:00 P.M. and at 100 mg/dl until 7:00 P.M. (2). The study was terminated at 24 h after the SC injection of glargine or detemir or earlier if plasma glucose increased to >180 mg/dl in the absence of glucose infusion. To ensure blinding, a simple randomization was used based on computer-generated random numbers by an individual who was not involved in establishing eligibility and entry of patients. Concealment of the randomization was ensured by having the allocation codes in a locked unreadable computer file handled by a designated investigator, who assigned subjects insulin cartridges corresponding to the 2 weeks of treatment (13). The same independent investigator gave subjects the SC injection of glargine or detemir insulin in all clamp studies by means of an insulin syringe in the abdominal area.

Analytical methods

Bedside plasma glucose was measured in triplicate using a Beckman Glucose Analyzer (Beckman, Palo Alto, CA). Plasma C-peptide was measured by radioimmunoassay (Linco Research, St. Charles, MO). Plasma insulin was measured using a two-site sandwich chemiluminescent immunoassay for human insulin (MLT, Cardiff, U.K.). The validation process with insulin glargine indicated that cross-reactivity is ~100% that of human insulin, whereas with insulin detemir the cross-reactivity is 200–300% that of human insulin. In all studies, plasma insulin was measured after extraction of antibodies with 30% polyethylene glycol (14). With this assay, greater values of insulin are expected with detemir than with glargine. In fact, insulin detemir is formulated with a greater molar ratio than human NPH and glargine (4:1:1, respectively), and, in addition, the assay does not distinguish between free and albumin-bound detemir, with the latter accounting for 98–99% of circulating levels (15). A1C was determined by high-performance liquid chromatography using an HI-Auto A_{1c} TM HA 8121 apparatus (DIC; Kyoto Daaichi Kogaku, Kyoto, Japan) (Diabetes Control and Complications Trial aligned nondiabetic subjects <6.1%). Plasma glycerol, β-hydroxybutyrate, lactate, and alanine were measured by previously described fluorometric assays (16). Plasma free fatty acid (FFA) concentrations were measured using a commercial kit (NEFA C test kit; Wako Chemicals, Neuss, Germany).

Calculations

Pharmacodynamic parameters of insulin action were calculated as follows: *1*) onset of insulin action: time at which IV glucose was initiated after SC insulin injection; *2*) minimal duration of action: time at which plasma glucose increased >118 mg/dl; *3*) end of action: time at which plasma glucose was consistently (for at least 30 min) >150 mg/dl; and *4*) end of study: time at which plasma glucose was consistently >180 mg/dl.

Insulin activity profile

Three variables account for insulin action during the pharmacodynamic clamp studies: *1*) the rate of IV insulin infusion (IIR), which may be needed in the initial part of the clamp study to compensate for the lag in onset of action of subcutaneously injected insulin with retarded activity; *2*) plasma glucose concentration; and *3*) the rate of glucose infusion (GIR) required to maintain the target plasma glucose. An ideal basal insulin should maintain the target plasma glucose concentration in the absence of GIR and/or IIR. We have modified the insulin activity profile formula by Radziuk et al. (17) that allows interpretation of simultaneous changes of plasma glucose (PG), GIR, and IIR after SC insulin injection, without determination of endogenous glucose production:

$$[(\text{Target PG}/\text{Actual PG})\ \%] + [(\text{Actual GIR}/\text{Total GIR})\ \%] - [(\text{Actual IIR}/\text{Baseline IIR})\ \%]$$

Statistical analysis

The linear trapezoidal rule was used to calculate the area under curve (AUC) for plasma insulin, plasma glucose, GIR, and nonglucose substrates. Maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) for the same variables were read directly from the plasma concentration-time data for each subject. GIR data were smoothed by taking a three-point moving average to provide reliable data for calculation of GIR C_{max} and GIR T_{max}. The primary analysis of the pharmacokinetic/pharmacodynamic parameters was performed on log-transformed data using ANOVA, which allowed for variation due to sequence, subjects nested within sequence, period, and treatment. The mean differences between treatments were estimated along with their 95% CIs. The ratios between antilogged treatment means and the corresponding antilogged

CIs were calculated. T_{max} variables, onset of action, duration of action, and end of action were analyzed nonparametrically. Wilcoxon's rank-sum test was used to perform crossover analyses, and Hodges-Lehmann estimates of the treatment effect were computed with 95% CIs (18,19). No significant treatment carryover effects were found for any of the data presented. Regression analysis on insulin concentrations after transformation to *Z* scores was done by using the least squares method. The primary end point of the study was time to end of action. With a sample size of 24 subjects, the two-sided test at the 5% significance level of a 2 × 2 crossover design had 80% power of detecting a difference of duration of action of 5 h between the treatments with the SD of the differences of 4 h. All tests of statistical hypothesis were carried out at the 5% level of significance, and comparisons were two-sided. Data in text are expressed as means ± SD and in figures as means ± SE. Statistical analysis was usually performed using NCSS/PASS (20).

RESULTS

All of the 24 subjects enrolled completed the two euglycemic clamp studies.

Glycemic control and insulin doses

Glycemic control (mean blood glucose from home monitoring data over days 1–14) was not different with glargine 131 ± 12 mg/dl or detemir 134 ± 9 mg/dl ($P = 0.417$). Total daily insulin dose (values over 3 days before studies) during treatment with detemir (0.70 ± 0.07 unit/kg) was higher than with glargine (0.65 ± 0.06 unit/kg) ($P = 0.001$), owing to a greater dose of rapid-acting analog with detemir (0.38 ± 0.05) than with glargine (0.33 ± 0.05 unit/kg, $P = 0.001$), primarily because of the need for more frequent correction boluses in the afternoon (0.03 ± 0.02 vs. 0.01 ± 0.02 unit/kg, $P = 0.007$). The dose of glargine (0.33 ± 0.02 unit/kg) was essentially the same as that of detemir (0.32 ± 0.03 unit/kg) ($P = 0.095$).

Plasma glucose levels immediately before lunch were 137 ± 24 and 133 ± 27 mg/dl for glargine and detemir, respectively ($P = 0.638$), and doses of rapid-acting analog before lunch were not different between treatments (0.12 ± 0.02 vs. 0.13 ± 0.03 unit/kg, glargine vs. detemir, $P = 0.263$). Similarly, plasma glucose before IV insulin infusion (2:30 P.M.) was no different for the two treatments (glargine 149 ± 49 mg/dl and detemir 145 ± 40 mg/dl, $P = 0.306$).

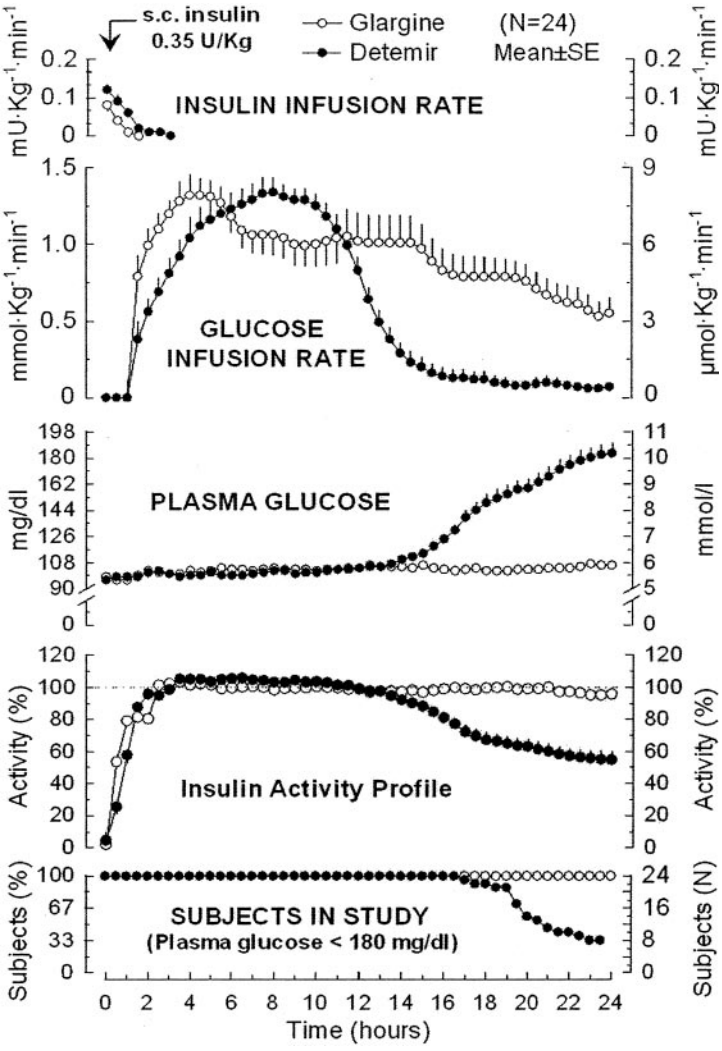

Figure 1—*Rates of IV insulin infusion, plasma glucose, rates of IV glucose infusion, insulin activity profile, and number of subjects in the study (plasma glucose <180 mg/dl, 10 mmol/l) after SC injection of insulin detemir or insulin glargine.*

Rates of IV insulin and glucose infusion, plasma glucose concentration, and insulin activity profile

The amount of regular insulin infused intravenously from −4.5 to 0 h (preinjection period) to maintain euglycemia was nearly twice as high with detemir (4.0 ± 1.7 units) than with glargine treatment (2 ± 1 units) ($P < 0.001$) (Fig. 1 and Table 1). After the SC injection of basal insulin at time 0 h (7:00 P.M.), the rate of IV insulin infusion remained greater with detemir (0.29 ± 0.40 mU · kg^{-1} · min^{-1}) vs. glargine (0.11 ± 0.19 mU · kg^{-1} · min^{-1}, $P = 0.038$). The median time of IV insulin withdrawal was longer with detemir (60 min [95% CI 0–90]) than with glargine (30 min [0–60]), but the difference was not statistically significant ($P = 0.145$).

The plasma glucose concentrations at time point 0 with detemir and glargine were similar (99.0 ± 5.5 and 100.0 ± 3.5 mg/dl, respectively, $P = 0.142$). During the first 12 h of the study, the two treatment groups had similar mean $AUC_{0-12\ h}$ values, corresponding to mean plasma glucose concentrations of 100.0 ± 1.9 and 101.0 ± 2.9 mg/dl with detemir and glargine, respectively ($P = 0.111$). Similarly, the between-subject variability of plasma glucose was low in both treatment groups (coefficients of variation <3.0%). In the second half of the study period (time 12–24 h), the mean plasma glucose concentration was higher with detemir

Table 1—*Onset of action and duration of action of insulin detemir and insulin glargine and pharmacodynamic variables after SC of insulin detemir and insulin glargine*

	Detemir	Glargine	Point estimate (%)*	*P* value
Onset of action (time at which GIR was started, h)	1.3 (1; 2)	1.3 (1; 3)	0 (−0.25 to 0.25)	0.818†
Minimal duration of action (time at which PG >118 mg/dl, h)	15.5 (13; 24)	24 (22; 24)	−7.75 (−8.5 to −6.75)	0.000†
End of action (time at which PG >150 mg/dl, h)	17.5 (16; 24)	24 (23; 24)	−4.5 (−6.2 to −3.25)	0.000†
End of study (time at which PG >180 mg/dl, h)	21.5 (17; 24)	24 (24; 24)	−2.25 (−3.3 to −1.5)	0.001†
AUC $GIR_{0–24\ h}$ (mg/kg)	915 ± 225	1,412 ± 662	70.3 (53.4 to 92.7)	0.015
AUC $GIR_{0–12\ h}$ (mg/kg)	773 ± 200	807 ± 352	97.7 (78.5 to 121.6)	0.832
AUC $GIR_{12\ h–end\ of\ infusion}$ (mg/kg)	142 ± 194	605 ± 390	17.4 (8.2 to 36.7)	0.000
GIR C_{max} ($mg \cdot kg^{-1} \cdot min^{-1}$)	1.6 ± 0.5	1.8 ± 0.6	90 (78.0 to 103.7)	0.137
GIR T_{max} (h)	7 (2; 12)	4 (1; 24)	3.25 (0.5 to 5.3)	0.035†

Data are means ± SD or median (min; max). $n = 24$. *Point estimates for treatment effect are based on the Hodges-Lehmann estimate of the median difference with the associated 95% CI (onset, minimal duration, end of action, end of study, and GIR T_{max}). Point estimates and 95% CIs for the ratio of treatment means are based on adjusted means derived from ANOVA (AUC $GIR_{0–24\ h}$, AUC $GIR_{0–12\ h}$, AUC $GIR_{12\ h–end\ of\ infusion}$, and GIR C_{max}). †*P* value from Wilcoxon's rank-sum test. PG, plasma glucose.

(137 ± 17 mg/dl) than with glargine (104 ± 4 mg/dl) ($AUC_{12\ h–end\ of\ study}$ 1,430 ± 221 vs. 1,248 ± 45 mg/dl, respectively, $P = 0.002$). Although onset of action was not different between the two insulins, the minimal duration of insulin action was shorter, with an end of insulin action and end of study time earlier with insulin detemir than with glargine (Table 1). By the end of the clamp study (time 24 h), with detemir insulin action had ended in 87% of subjects, but only in 8% of subjects treated with glargine (Fig. 1 and Table 1). Because the study was interrupted at 24 h, the duration of insulin action cannot be estimated beyond this time point for those subjects whose plasma glucose levels remained <150 mg/dl at 24 h (underestimation). Pharmacodynamic variables calculated from the GIR of Fig. 1 are shown in Table 1. The mean GIR for the 24-h study period ($AUC_{0–end\ of\ GIR}$) was greater with glargine than with detemir. However, over the initial 12-h period ($AUC_{0–12\ h}$), the GIR with glargine and detemir were equivalent. The mean GIR for the second 12-h period ($AUC_{12\ h–end\ of\ GIR}$) was lower by ~80% with detemir compared with glargine. Although GIR C_{max} values were similar with the two basal insulin analogs with no distinct peak, maximum insulin activity (GIR T_{max}) was reached at a median time of 7 h after treatment with detemir and 4 h after treatment with glargine. The insulin activity profiles, as derived from the described formula (see RESEARCH DESIGN AND METHODS), indicated an earlier and greater activity throughout the study with insulin glargine (108 ± 30%) than with detemir (60 ± 29%) ($P < 0.01$).

Plasma insulin and substrate concentrations

As expected, the overall plasma insulin concentrations were higher with detemir than with glargine (Fig. 2 of the online appendix [available at http://dx.doi.org/10.2337/dc07-0002]). Within-treatment comparisons indicated that insulin levels (AUC) were higher during the first 12-h period than during the second 12-h period of the study, both with detemir (4,572 ± 1,478 vs. 2,209 ± 1,105 μU/ml, $P < 0.001$) and with glargine (420 ± 202 vs. 332 ± 138 μU/ml, $P < 0.001$). However, the rate of plasma insulin disappearance was 5 times greater for insulin detemir than glargine (Z scores −2.40 ± 0.15 vs. −0.50 ± 0.05, respectively, $P < 0.001$).

Plasma concentrations of substrates indicating primarily lipolysis (FFA and glycerol) and ketogenesis (β-hydroxybutyrate) were higher with detemir than with glargine from 12 h to the end of study. In fact, FFA, glycerol, and β-hydroxybutyrate were, respectively, 29% (95% CI 11–44, $P = 0.004$), 22% (4–37, $P = 0.023$), and 52% (28–68, $P = 0.001$) greater with detemir. In addition, FFA was greater with detemir also during the initial 12 h (33% [95% CI 15–47], $P = 0.002$). Lactate concentrations were not different between treatments. Overall, alanine levels decreased with both treatments, although they were 9% (95% CI 3–14, $P = 0.007$) higher with detemir than with glargine.

CONCLUSIONS

— The present report describes the pharmacokinetics and pharmacodynamics of insulin analogs detemir and glargine at steady state in subjects with type 1 diabetes in response to a dose reproducing closely to that used during the 2 weeks before studies to optimize postabsorptive plasma glucose. The end of action was earlier with detemir than with glargine, whereas the onset of action was no different (Table 1). Because the study terminated at 24 h, the end of action is underestimated in those subjects (13% with detemir and 92% with glargine) whose plasma glucose remained <150 mg/dl by 24 h.

In the present study, we propose "minimal end of action" as a meaningful pharmacodynamic parameter for estimating activity of basal insulin. An ideal basal insulin should restrain endogenous glucose production to keep fasting plasma glucose <100 mg/dl. A criterion of "minimal duration of action" (time at which plasma glucose is >118 mg/dl) may help more than "end of action" (plasma glucose >150 mg/dl) in understanding the appropriateness of the replacement of basal insulin in subjects with diabetes treated to target (21).

With regard to the definition of the onset of action and the target plasma glucose of the clamp, the present study is different from previous studies (2,22). In fact, because of the ongoing activity of basal insulin injected the day(s) before, the definition of the onset of action has been based on the time of initiation of GIR rather than on the change in the rate of IV insulin. In addition, the target plasma glucose of the clamp has been lowered from 130 to 100 mg/dl, the latter being the currently accepted goal of fasting glucose in intensive insulin treatment.

One of the most important metabolic

actions of insulin is to prevent lipolysis (23). In the present study, the duration of the antilipolytic action of the subcutaneously injected long-acting insulin analogs differs, with plasma FFA increasing earlier with detemir than with glargine, even during the initial 12 h of study, at which time activities of detemir and glargine on glucose metabolism were equivalent. Similarly, plasma β-hydroxybutyrate increased to >3.0 mmol/l by the end of study with detemir but only to ~1.5 mmol/l with glargine. Overall, the antilipolytic activity of detemir was lower than that of glargine (Fig. 2 of the online appendix). This result reflects the in vitro data, which indicate that detemir is estimated to possess only ~27% lipogenic potency versus human insulin (24). Despite concentration to a molar ratio of 5:1 versus NPH in normal, nondiabetic subjects (25) and to 4:1 versus glargine in type 1 diabetic subjects (present study), detemir still exhibits lower antilipolytic effect (25). These observations might explain in part the reported smaller weight gain with detemir than with NPH in type 1 diabetes after adjustment for changes in A1C (26).

To the best of our knowledge, this is the first study comparing the potency of detemir and glargine in subjects with type 1 diabetes. In the present study, 1 unit of detemir (24 nmol insulin) was ~30% less active than 1 unit of glargine (6 nmol insulin) in terms of total glucose infused. This would explain, at least in part, the shorter end of action and lower antilipolytic effect of detemir. If confirmed, these results would indicate that in type 1 diabetes detemir reaches bioequivalence to glargine at a molar ratio greater than the currently formulated 4:1 versus human insulin. Interestingly, in normal, nondiabetic subjects equipotency has been reported with a molar ratio of detemir to NPH of 5:1 (25).

Traditionally, in clamp studies insulin action has been derived by the rate of glucose infusion (2–4). However, GIR does not totally reflect insulin action either in the early or in the late part of the clamp. In the early part, IV insulin infusion is the (negative) indicator of subcutaneously injected insulin. Later, when GIR decreases and becomes 0, the rate of increase in plasma glucose indicates (negatively) the action of subcutaneously injected insulin. The activity profile formula (see RESEARCH DESIGN AND METHODS) allows estimates of onset of insulin action better than those derived solely from the GIR. The activity profiles of detemir and glargine exhibit a similar plateau between 2 and 13 h, after which glargine remains at a steady activity close to 100% until the end of the 24-h study period, whereas with detemir a progressive decrease in activity was observed after 12 h, reading 55% at 24 h. In the present study, subjects without endogenous insulin secretion (type 1 diabetes) have been studied to specifically assess the effect of the pharmacokinetic/pharmacodynamic profile of the subcutaneously injected "basal" insulin analogs glargine and detemir. The presence of endogenous insulin secretion, either normal (nondiabetic subjects) or impaired (type 2 diabetes), contributes, to some extent, to the action of insulin injected subcutaneously; therefore, the interpretation of such results is limited. Also, because of the large interindividual differences in pharmacokinetics and pharmacodynamics (3), it is more important to conduct crossover, not parallel group, studies (3,27). These considerations are likely to account for the different findings for pharmacokinetics and pharmacodynamics in the present study compared with those in previous studies in type 2 diabetes (28), especially with parallel groups (27).

In one study in type 1 diabetes (3), with an insulin dose greater than that in the present study (0.4 vs. 0.35 unit/kg), glargine exhibited median end of action at 24 h and detemir at 23 h (T. Heise, personal communication), whereas it was 4.5 h (median time) longer for glargine in the present study (Table 1). However, it is difficult to compare the results of Heise et al. (3) with those of the present study because of the different study design and their use of the biostator. In the study by Plank et al. (22) replicating the clamp method of our previous study (2), a full dose response of progressively increasing dose of detemir from 0.1 up to 1.6 units/kg was elegantly described. In that study (22), however, insulin doses <0.4 unit/kg (0.1 and 0.2 unit/kg) showed that the end of action data were asymmetrically distributed with positive skewness (mean values greater than median values; T. Pieber, personal communication), as they are in our study using 0.35 unit/kg. In fact, in our study, the mean and SD values of the end of action for insulin detemir were 19.4 and 2.9 h, respectively, and the median was 17.5 h. Conversely, in the study by Plank et al. (22), 0.4 unit/kg (or higher doses) of detemir resulted in a longer end of action in the majority of subjects studied as indicated by greater median values (22.7 h) than mean ± SD values (21.5 ± 3.3 h). Therefore, in addition to the different population studied, the simplest explanation to reconcile the longer (22) with the shorter median of present study (Table 1) is the higher detemir dose used by Plank et al. (22). Also, methodological differences between the study of Plank et al. (22) and the present study, such as the different plasma glucose target (130 vs. 100 mg/dl, respectively) and the steady-state condition (present study) versus first dose (22), may have the affected calculation of end of action. The latter difference is important when long-acting insulin analogs are studied because with glargine the end of action is different after the first dose versus after 1 week of use (4). However, the aim of the present study was not to reestablish the end of action of detemir or glargine individually in "absolute" terms; rather it was to compare the pharmacokinetics and pharmacodynamics of the two basal insulins "relatively" to each other, when tested at the doses used by subjects with type 1 diabetes in a study to optimize every day postabsorptive plasma glucose.

The pharmacokinetic and pharmacodynamic findings of the present study indicate that glargine should be once-daily basal insulin in subjects with type 1 diabetes, whereas detemir appears to be twice-daily basal insulin in the majority of subjects. However, the question of clinical use of detemir is open to debate. A clinical trial has shown noninferiority with detemir given once daily compared with twice daily in type 1 diabetes in terms of percentage of A1C (29). In an observational trial, 49% of subjects with type 1 diabetes were treated with detemir once daily (30). On the other hand, several trials designed to optimize replacement of basal insulin needs with detemir have used detemir twice daily in type 1 diabetes (26,31). In the small group of subjects of the present study followed for 2 weeks, detemir was successfully used once daily, but the dose of rapid-acting insulin at lunch was increased more, and a correction bolus in midafternoon was given more frequently than with glargine. Additional studies exploring optimized regimens of detemir insulin in type 1 diabetes are needed.

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