Pediatric Diabetes 2008: 9: 554–560
doi: 10.1111/j.1399-5448.2008.00443.x

Pediatric Diabetes

Original Article

Insulin detemir is characterized by a more reproducible pharmacokinetic profile than insulin glargine in children and adolescents with type 1 diabetes: results from a randomized, double-blind, controlled trial*

Danne T, Datz N, Endahl L, Haahr H, Nestoris C, Westergaard L, Fjording MS, Kordonouri O. Insulin detemir is characterized by a more reproducible pharmacokinetic profile than insulin glargine in children and adolescents with type 1 diabetes: results from a randomized, double-blind, controlled trial.
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Abstract: Insulin detemir (detemir) has previously been shown to be associated with lower within-subject variability compared with other basal insulin preparations in adults with type 1 diabetes mellitus (T1DM). This randomized, double-blind, crossover trial compared the within-subject variability of detemir and insulin glargine (glargine) in pharmacokinetic properties in children and adolescents with T1DM. The trial enrolled 32 children and adolescents (19 girls and 13 boys; mean ± SD: age 13 ± 2.5 yr and T1DM duration 6.3 ± 3.0 yr) with a hemoglobin A1c (HbA1c) of 7.9 ± 1.0%. Participants were randomized to a specific treatment sequence in which a dose of 0.4 U/kg of detemir and glargine was injected subcutaneously 24 h apart at each of two dosing visits. Insulin concentrations were measured at frequent intervals for a period of 16-h post-dosing. Detemir showed statistically significantly less within-subject variability compared with glargine with a 3.1-fold and 2.9-fold lower coefficient of variation (CV, %) for the area under the concentration–time curve [$AUC_{(0–16\ h)}$] and the maximum concentration (C_{max}), respectively. Separate analyses demonstrated a 2.5-fold and 2.9-fold lower CV (%) with detemir in children (8–12 yr) and a 4-fold and 3.8-fold lower CV (%) with detemir in adolescents (13–17 yr). No safety concerns were raised during the trial. In conclusion, within-subject variability in pharmacokinetic properties was significantly lower for detemir than for glargine in children and adolescents with T1DM. This indicates a less variable absorption with detemir, which is expected to be associated with a more predictable therapeutic effect also in this population.

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Key words: insulin detemir – insulin glargine – pediatric – type 1 diabetes – within-subject variability

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Submitted 20 April 2008. Accepted for publication 13 June 2008

*The results of this study have been previously published as an abstract at the EASD 2007.

Good glycemic control is of utmost importance in pediatric subjects with type 1 diabetes mellitus (T1DM) who are facing a lifelong disease. The Diabetes Control and Complications Trial (DCCT) has shown that intensive insulin therapy can optimize glycemic control and minimize long-term complications in both adults (1) and adolescents (2, 3). While the hemoglobin A1c (HbA1c) for the time being remains the gold standard for assessing the risk of late complications, it has obvious limits as it is only a parameter for average glucose levels. Evidence is building relating to the importance of glycemic variability for various outcomes in T1DM (4).

Recently, new insulin analogues with potential benefits compared with older insulin preparations have been developed and investigated mainly in adults. However, the limited information trials involving children and adolescents suggest that the advantages associated with these analogues are also observed in pediatric subjects. In some cases, the younger age-groups may benefit further from the use of such therapies because of a more pronounced variation in lifestyle patterns compared with adults. Examples include the injection of rapid-acting analogues with the actual meals (5), lower risk of nocturnal hypoglycemia with basal analogues because of a less pronounced peak effect (6, 7), and homogenous soluble preparations administered with easy-to-use pen systems.

Detemir and glargine are both soluble basal human insulin analogues with unique modes of protraction. For detemir, the protracted effect is caused by a combination of increased self-association at the injection site and binding to albumin in the subcutis as well as in the blood stream (8). With glargine, the protracted action is related to a shift in the isoelectric properties upon subcutaneous (s.c.) injection, which brings about formation of micro-precipitates from which small amounts are slowly released (9). Previous trials in adults have shown that the within-subject variation in pharmacokinetic and pharmacodynamic properties is lower with detemir than with glargine, indicating a more reproducible day-to-day insulin absorption and glucose-lowering effect with detemir (10, 11). The aim of this study was to compare the within-subject variability of the pharmacokinetic profiles of detemir and glargine in children and adolescents with T1DM.

Methods

Patients

The selection criteria of the study included boys and girls aged 6–17 yr with T1DM $\geq$1 yr, HbA1c $<$11%, body mass index (BMI) of 15–24 kg/m^2 for 6–12 yr and 18–29 kg/m^2 for 13–17 yr and treated with insulin at a total daily dose of $\geq$0.6 IU/kg without any significant diseases including hepatic or renal disorders, microalbuminuria, or retinopathy. Subjects using systemic prescription drugs apart from insulin or who had donated $>$500 mL blood within the past 12 months were also excluded. The aim was to include an equal number of children (6–12 yr) and adolescents (13–17 yr). Twelve years was chosen as the upper age limit for children because previous trials have indicated that puberty occurs later in children with T1DM than in non-diabetic subjects (12).

The sample size was determined based on the variation observed in an earlier clinical trial comparing the within-subject variation between detemir and glargine in adult subjects (10). It was estimated that 24 subjects and two replications on each insulin preparation per subject would provide a power of 80% to detect a ratio in coefficient of variation (CV, %) of 3.33 for area under the concentration–time curve (AUC) [$AUC_{(0–16\ h)}$]. A total of 32 subjects were included to adjust for anticipated dropouts.

The trial was approved by the local ethical committee and was performed in accordance with Good Clinical Practice and the Declaration of Helsinki (13) and with guidelines set forth by the Committee for Proprietary Medicinal Products (CPMP) at initiation of the trial. Written informed consent was obtained from all participants (or their parents or legally accepted representatives, if applicable) before any trial-related activities.

Protocol

After an initial screening visit, eligible subjects were assigned the lowest available randomization number within the age-group of 6–12 or 13–17 yr. Participants were randomized to a specific treatment sequence and attended two dosing visits, each lasting around 44 h (Friday evening until Sunday afternoon). On each dosing visit, subjects received both trial products (detemir on day 1 and glargine on day 2 or vice versa according to the randomization scheme) (Fig. 1). Subjects attended the clinic in the afternoon and were asked to stop the running basal rate of their insulin pump as all enrolled subjects were treated with continuous subcutaneous insulin infusion (CSII).

To minimize the number of visits to the clinic, subjects were dosed over the weekend with both insulin preparations at an interval of 24 h. Although this could be considered an insufficient washout period, the risk of a carryover effect was eliminated by use of assays specific for detemir and glargine. A 16-h sampling period after trial drug administration was considered adequate as this covers the main absorption period and was chosen to minimize loss of blood volume and for practical reasons to allow subjects to leave the clinic on Sunday afternoon.

Human soluble insulin (Actrapid®, 100 IU/mL; Novo Nordisk AS, Bagsvaerd, Denmark) was infused intravenously to achieve blood glucose levels between 5.5 and 10 mmol/L but was stopped before s.c. injection of

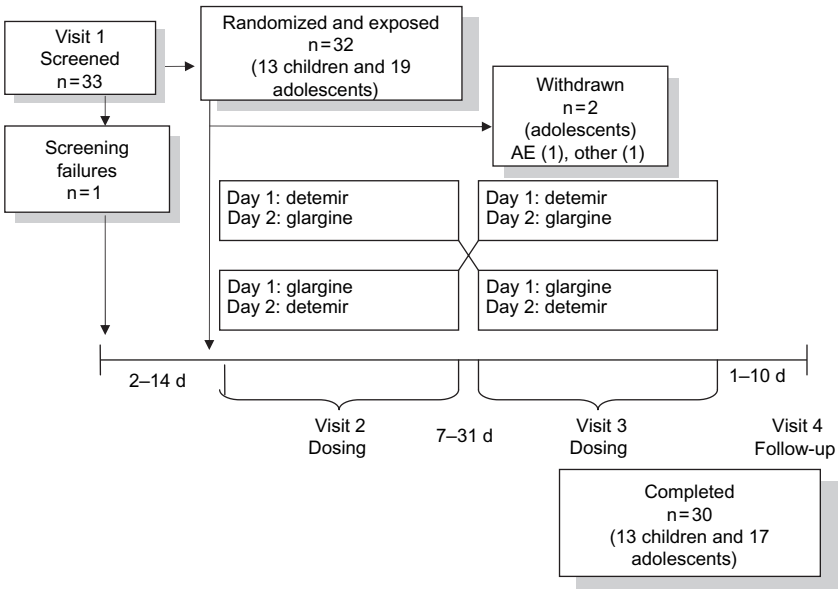

Fig. 1. Subject disposition and trial diagram outlining the crossover design at dosing visits.

trial drug to avoid hypoglycemia. A qualified person (not otherwise involved in the trial) performed the preparation and administration of trial drug to ensure double-blinding. A dose of 0.4 U/kg of detemir [Levemir®, 100 U/mL (2400 nmol/mL); Novo Nordisk AS] or glargine [Lantus®, 100 U/mL (600 nmol/mL); Sanofi Aventis, Frankfurt, Germany] was administered s.c. in the thigh using a pen device at 24-h intervals. This dose was identical to the dose used in previous trials (10, 11) and is within the normal dose range for basal insulin products. The composition of meals and the level of activity were kept constant during the two dosing days and carbohydrate intake was recorded. Subjects were allowed to take s.c. insulin aspart (NovoRapid®, 100 U/mL; Novo Nordisk AS) at meals or if blood glucose $\geq$14 mmol/L 2-h post-meal or during the night at the investigators discretion.

Blood samples were drawn for determination of detemir and glargine concentrations in plasma at 0 (just before dosing), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, and 16 h. Blood glucose was monitored every hour for the first 10 h after administration of trial drug and thereafter every second hour until the next trial product injection or until the last blood sample had been taken (last dosing visit). Fertile females performed pregnancy tests during the trial.

Plasma concentrations of detemir (albumin-bound plus albumin-free fraction) and glargine were measured by use of immunoassays specific to detemir or glargine with no cross-reaction to other insulins. The lower limit of quantification (LLOQ) was 25 and 15 pmol/L for the detemir and glargine assays, respectively. Both assays were within the specifications set forth by Food and Drug Administration (FDA).

Adverse events (AEs) were monitored during the trial, and standard laboratory parameters, physical examination, and vital signs were recorded at screening and at the end of the trial. Information regarding pubertal status, weight, height, and BMI was also collected. Subjects followed their usual insulin treatment between the two dosing visits.

Statistical analyses

Pharmacokinetic end-points included the area under the insulin concentration curve from 0 to 16 h [$AUC_{(0–16\ h)}$], from 0 to 5 h [$AUC_{(0–5\ h)}$], maximum concentration (C_{max}), and time to maximum concentration (t_{max}). These were estimated from the individual plasma concentration–time profiles. AUC was approximated using the trapezoidal technique. Within-subject variability of pharmacokinetic end-points between detemir and glargine was analyzed in an analysis of variance with mean value depending on insulin preparation and treatment period, subject, and interaction between subjects and insulin preparation as random effects and an error term. Logarithmically transformed end-points were used to account for increasing variance with increasing concentration of trial drug. The null hypothesis was that the within-subject variability was the same for the two insulin preparations (i.e., the ratio between the variances was equal to 1). Within-subject variability is presented as CV, calculated using the properties of the log-normal distribution. Individual detemir and glargine plasma concentration values below LLOQ were treated as missing. SAS® (SAS Institute, Cary, NC, USA) release 8 or higher was used for all analyses.

Results

Of the 33 subjects screened, 32 were randomized and received treatment (Fig. 1). Two subjects (both adolescents) were withdrawn from the trial after the first dosing visit; one because of an AE (thrombophlebitis) and the other because of poor venous access. The remaining 30 subjects completed the trial and were included in the per protocol pharmacokinetic analyses.

Baseline characteristics are shown in Table 1. All 19 adolescents and 6 children (46%) were pubertal, Tanner stage 2 or more. All participants were Caucasians and were non-smokers apart from one adolescent. At trial entry, all participants were on CSII therapy; 15 with insulin aspart (NovoRapid) and 17 with insulin lispro (Humalog®).

Mean t_{max} was (mean ± SD) 7 ± 2 h for detemir and 9 ± 4 h for insulin glargine overall, with an identical mean for both children (7 ± 3 vs. 9 ± 4 h) and adolescents (7 ± 2 vs. 9 ± 4 h). Baseline concentrations were not reached within the 16-h sampling period for any of the insulin preparations (Fig. 2), but the concentration of detemir appeared to decrease earlier than for glargine. Within-subject variability, as measured by CVs, was lower for detemir than for glargine with regard to $AUC_{(0–16\ h)}$, $AUC_{(0–5\ h)}$, and C_{max}, and the ratios between the variances (glargine/detemir) were statistically significantly different from 1 ($p < 0.0001$). The significantly lower variability of insulin detemir seen in the whole population was maintained when children and adolescents were analyzed separately ($p < 0.003$ for all pairwise comparisons, Fig. 3).

A total of 39 AEs were reported in 26 subjects during the trial, 18 events in 13 subjects during treatment with detemir and 21 events in 13 subjects during treatment with glargine. All events were considered as having an unlikely relation to trial products. The vast majority of AEs were related to feelings of discomfort including headache, dizziness, increased body temperature, and malaise. In addition, two injection-site disorders and two hypoglycemic episodes were reported after administration of glargine. Five events were of moderate severity, while the rest were mild. One serious AE unrelated to the trial drug administration was reported: a 10-yr old girl experienced thrombophlebitis in the right arm (at the site of the cannula for drawing the blood) after the second dosing (glargine) at the first visit and was withdrawn from the trial. Another subject was withdrawn because of dizziness and syncope (both moderate) after administration of detemir.

Overall, the AE profiles were similar for children and adolescents and for detemir and glargine, and no clinically relevant findings in other safety parameters were reported.

Discussion

Lower within-subject variation with detemir compared with glargine has previously been reported in adult subjects with T1DM (10, 14) and type 2 diabetes mellitus (T2DM) (11). In these trials, glucose infusion rates were assessed to estimate variability in pharmacodynamic responses as the variation in blood-glucose-lowering properties of the two insulin analogues are generally considered of primary interest (15). However, for ethical reasons (such as the amount of blood withdrawn), it is not possible to perform clamp studies in children, and therefore, pharmacokinetic rather than pharmacodynamic variability was evaluated as the primary outcome of this trial.

Differences in insulin absorption are an important aspect of insulin treatment affecting glycemic control, duration of action, and risk of hypoglycemia (16). Previously, a lower variability between subjects in pharmacokinetic parameters was demonstrated with detemir compared with neutral protamine Hagedorn (NPH) insulin across different age-groups (17). The results of the current trial show that the lower variability observed with detemir is caused by a more predictable absorption within individual subjects. Furthermore, variation in pharmacokinetic parameters was also assessed in the study by Heise et al. (10), and as shown in Table 2, the within-subject variation observed in the current trial for pediatric subjects was very similar to that observed in adult subjects treated with detemir. The similarities between these results and those found in adults indicate that the lower variation observed with detemir is likely also to be reflected in the pharmacodynamic parameters. This is supported by findings

Table 1. Patient baseline characteristics

	Children	Adolescents	All
Gender (F/M)	6/7	13/6	19/13
Age (yr)	11 (8–12)	15 (13–17)	13 (8–17)
Duration of diabetes (yr)	5.2 (1–11)	7.0 (1–11)	6.3 (1–11)
Weight (kg)	42 (31–60)	64 (52–77)	55 (31–77)
BMI (kg/m^2)	19.4 (16.1–22.6)	22.8 (17.7–28.6)	21.4 (16.1–28.6)
HbA1c (%)	8.0 (6.9–10.1)	7.9 (6.5–9.6)	7.9 (6.5–10.1)

BMI, body mass index; F, female; HbA1c, hemoglobin A1c; M, male.
Values indicate number of subjects or mean value and range.

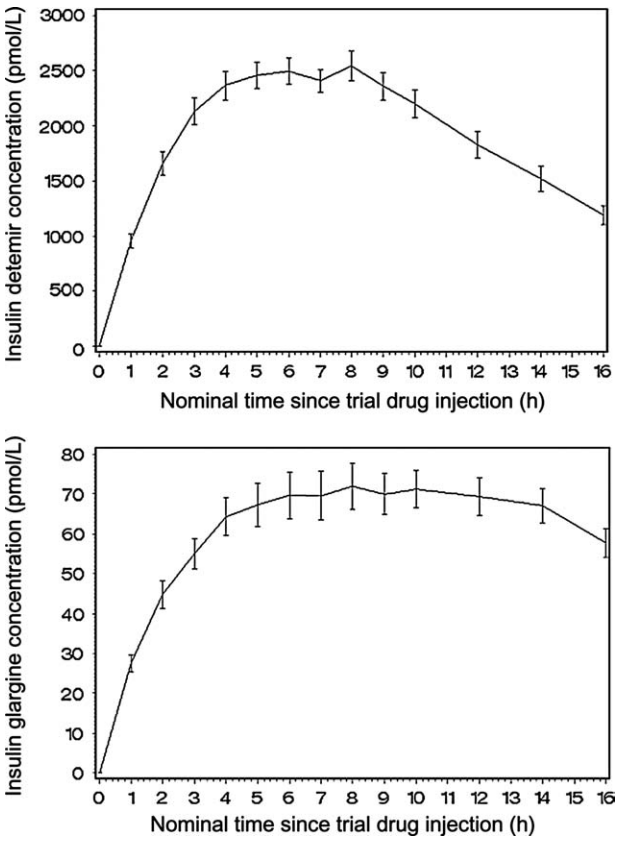

Fig. 2. Mean concentration–time profiles (±SEM) for insulin detemir (top panel) and insulin glargine (lower panel).

from a study by Robertson et al. in which children and adolescents treated with detemir demonstrated a lower within-subject variation in home-measured fasting plasma glucose and a lower risk of nocturnal hypoglycemia than those treated with NPH at comparable levels of HbA1c (6). In a recent meta-analysis of four trials with the long-acting insulin detemir, a significant correlation between the inpatient variability (coefficient of variation) of fasting blood glucose and the rate of hypoglycemia was found (18).

In the Berlin Retinopathy Study, some adolescents developed retinopathy after a relatively short duration of diabetes despite a good long-term HbA1c (19). It is now known from continuous glucose monitoring that the HbA1c does not reflect the true blood glucose variations in children (20); thus, a high glycemic variability despite good HbA1c would offer an explanation for early pediatric retinopathy. In the DCCT study, intensified insulin regimens known to lead to more physiological insulin levels were associated with less retinopathy at the same level of HbA1c compared with conventional two-injection treatment (21). Consequently, intensified insulin regimens such as basal–bolus therapy or CSII are the preferred treatment options for pediatric subjects (22). Insulins that are able to contribute to a reduced glycemic variability may therefore be of relevance also for the long-term outcomes in pediatric diabetes.

Guidelines for the treatment of diabetes in pediatric subjects recommend an HbA1c <7.5% (23). This target appears to be hard to achieve, and several studies have shown that HbA1c is often >8% (24). In general, children and adolescents represent a group of patients who are difficult to treat because of variation in eating and exercise pattern, growth, and fluctuations in hormone concentrations. Furthermore, compliance with insulin therapy may be poor in some subjects because of fear of hypoglycemia or weight gain. A lower variation in insulin absorption is of major importance also in pediatric subjects as this would allow further optimization of insulin treatment without additional risk of hypoglycemia. Moreover, a lower variation of insulin levels is likely to reduce glycemic variability, which is currently debated as a significant contributor to late complications independent of HbA1c (4). For example, in patients with T2DM, a significant association of the mean amplitude of glycemic excursions, an established parameter for glycemic variability (25), and urinary 8-iso-prostaglandin F2 (PGF2) alpha, a parameter related to superoxide overproduction and subsequent development of later complications, was reported (26). Another important effect of glucose fluctuations in children was revealed with continuous glucose monitoring. It provided proof of the association of fluctuating blood glucose levels and behavioral changes that parents report frequently in their diabetic children (27).

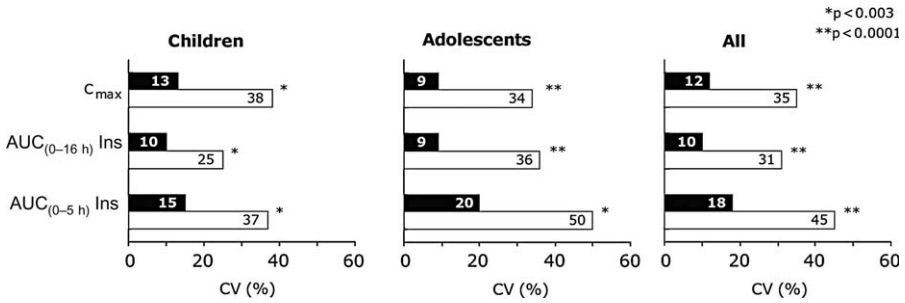

Fig. 3. Within-subject variation [CV (%)] in pharmacokinetic end-points with detemir and glargine. Black boxes, detemir; white boxes, glargine. AUC, area under the concentration–time curve; C_{max}, maximum concentration; CV, coefficient of variation.

Table 2. Within-subject coefficient of variation in pediatric subjects compared with adults

		Children and adolescents (%)	Adults (%) (10)
C_{max} (pmol/L)	Detemir	12	18
	Glargine	35	34
$AUC_{(0–16\ h)}$ (pmol·h/L)	Detemir	10	14*
	Glargine	31	33*
$AUC_{(0–5\ h)}$ (pmol·h/L)	Detemir	18	ND
	Glargine	45	ND

AUC, area under the concentration–time curve; C_{max}, maximum concentration; ND, not determined.
*The results stated in this study are calculated as $AUC_{(0-\infty)}$.

For some patients, a decreased amount of glycemic instability alone, even without any improvement in HbA1c, might represent an improved outcome. This suggests that different therapeutic strategies now in use for the pediatric population (28) should be evaluated for their potential to minimize glycemic excursions as well as their ability to lower HbA1c.

Insulin detemir and insulin glargine are different chemical entities dosed in different molar doses, and comparison between plasma concentration levels is therefore not meaningful. Maximum plasma concentration was reached after 6–8 h for insulin detemir and after 8–10 h for insulin glargine. Thereafter, plasma concentration declined, but baseline was not reached within the 16-h sampling period for any of the insulin preparations. Detemir and glargine have a duration of action of around 24 h and are recommended for once daily use (15), but detemir can be administered twice daily if needed adding flexibility for subjects with variation in day-to-day activities.

In conclusion, within-subject variability in pharmacokinetic properties was statistically significantly lower for insulin detemir than for insulin glargine in children and adolescents with T1DM. This indicates a less variable absorption with insulin detemir, which is expected to be associated with a more predictable therapeutic effect that may be meaningful in reducing glycemic variability and risk for hypoglycemia in this population.

Acknowledgements

We thank Kerstin Walte, RN, and Bärbel Aschemeier, RN, MPH, for practical and organizational assistance in the conduct of the study and Christoph Koenen, MD, Novo Nordisk A/S, Denmark; Eva Maaßen-Quotschalla, Novo Nordisk Pharma GmbH, Germany; Sarah Abrell, Novo Nordisk Pharma GmbH, Germany; and Lars H. Damgaard, PhD, Novo Nordisk A/S, Denmark, with assistance in data collection and evaluation. We thank Tina Rambrand for editorial assistance in preparation of the manuscript. This trial was sponsored by Novo Nordisk A/S.

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