Insulin Detemir Is Characterized by a Consistent Pharmacokinetic Profile Across Age-Groups in Children, Adolescents, and Adults With Type 1 Diabetes

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OBJECTIVE — This trial aimed to characterize for the first time the pharmacokinetic profile of insulin detemir, the novel soluble basal insulin analog, in children and adolescents compared with adults. Comparisons were also made with NPH insulin to determine any between-treatment difference in the effect of age on pharmacokinetic profile.

RESEARCH DESIGN AND METHODS — This single-center, open-label, randomized, crossover trial included children (aged 6–12 years, $n = 13$), adolescents (aged 13–17 years, $n = 10$), and adults (aged 18–65 years, $n = 11$) of both sexes. Subjects were given single doses of 0.5 units/kg s.c. insulin detemir or 0.5 IU/kg NPH insulin on 2 separate days. Serial blood sampling was performed for 24 h for analysis of serum insulin detemir, human insulin, and glucose concentrations.

RESULTS — The mean pharmacokinetic profile of insulin detemir was similar across all three age-groups. This was determined by statistical analyses of the data, which showed no overall age effect or between-group differences when pairwise comparisons were made between children (or adolescents) and adults on the parameters of the area under the curve (AUC), AUC from zero to infinity, AUC from 0 to 24 h [$AUC_{(0-24\ h)}$], and the maximum concentration measured during the 24 h after closing. No overall age effect for $AUC_{(0-24\ h)}$ and C_{max} was detected for NPH insulin, but data were only analyzable from seven adults and pairwise comparisons did indicate that children and adults had different pharmacokinetic profiles. Less total variability in the pharmacokinetics of insulin detemir than NPH insulin was indicated by lower coefficients of variation in AUC, C_{max}, and time to maximum concentration in all three age-groups.

CONCLUSIONS — The data suggest that insulin detemir can be used in children and adolescents with type 1 diabetes using titration guidelines similar to those used in adults. Moreover, insulin detemir may offer the advantage of greater predictability of response in comparison to NPH insulin due to lower total variability and a lesser degree of kinetic disparity across age-groups.

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Abbreviations: AUC, area under the curve; CV coefficient of variation; ELISA, enzyme-linked immunosorbent assay; MRT, mean residence time.

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

Large-scale intervention and outcome studies have shown that intensified treatment aimed at tight glycemic control helps to delay onset and slow progression of diabetes complications in children and adolescents and adults (1,2). Thus, basal-bolus insulin therapy aims to optimize glycemic control by limiting postprandial hyperglycemia using a short- and rapid-acting insulin formulation while sustaining basal insulin levels using an insulin with protracted absorption. This approach aims to mimic the diurnal insulin pattern seen in normal physiology. It is effective when compliance is maintained but requires multiple injections, close monitoring, and high motivation. Therefore, compliance is a challenge, particularly for children.

The effectiveness of basal-bolus therapy is also limited by inappropriate insulin absorption profiles. In the case of basal insulins, traditional formulations, such as NPH insulin and ultralente, are characterized by peaks in plasma concentration (3) that may result in hypoglycemia during the night and at other times, unless food intake can be timed to compensate. Children and adolescents are at particular risk of nocturnal hypoglycemia (4). In addition, variability in the absorption rate of injected insulin can also add to the risk of hypoglycemia and hence undermine compliance and glycemic control (5). Again, this may be a particular issue with basal insulins; as much as 80% of the daily variation in blood glucose concentration within and between patients taking NPH insulin is attributed to variation in insulin absorption (6). Moreover, the suspended formulas in which basal insulins are currently available require adequate agitation before use to ensure a homogenous mix, introducing user-dependent variability (7).

In recent years, genetically engineered insulin analogs have been intro-

Table 1—*Demographic characteristics of study population by age-group*

	Children (aged 6–12 years)	Adolescents (aged 13–17 years)	Adults (aged 18–65 years)
Male/female (*n*)	5/8	5/5	6/5
Age (years)	10.4 ± 1.2	15.1 ± 1.1	22.8 ± 6.4
Weight (kg)	36.5 ± 5.3	62.6 ± 6.8	76.5 ± 6.7
BMI (kg/m^2)	17.9 ± 1.1	21.1 ± 1.5	23.4 ± 1.9
Duration of diabetes (years)	2.9 ± 1.4	8.1 ± 4.0	9.8 ± 3.3
HbA_{1c} (%)	7.3 ± 0.9	8.1 ± 1.2	7.7 ± 1.0

Data are means ± SD or *n*.

duced in an attempt to refine and fully realize the potential of multiple-injection insulin therapy. Rapid-acting analogs, such as insulin aspart and insulin lispro, attempt to mimic the prandial insulin profile of normal physiology and are now widely used as the bolus component of basal-bolus therapy (8). These are also increasingly used in pediatric diabetology because they may offer potential benefits for problems frequently encountered in children, such as unpredictable eating patterns (9–11). Yet the advantages of treatment with rapid-acting insulin analogs can only be fully realized when replacement of basal insulin is also optimized, and to this end, basal analogs are now also being developed. The first of these to be introduced into clinical practice, insulin glargine, has a superior mean pharmacokinetic profile to NPH insulin (12–14) in adults but is presented in an acidic formulation that forms a precipitate in neutral environments, possibly contributing to a variable absorption profile (5,8).

Insulin detemir [Lys^{B29}(N^{ϵ}-tetradecanoyl) des(B30) human insulin] is another long-acting basal insulin analog that is soluble at neutral pH and hence may offer practical advantages. Detemir is characterized by the removal of threonine at position B30 and the acylation of a 14-carbon myristoyl fatty acid to lysine at position B29. The acylation of detemir enables albumin binding, which contributes to a protracted action (15). Data in healthy subjects show that insulin detemir has a flatter time-action profile than NPH, reaching its peak concentration nearly 90 min later (16), but its kinetic profile has only been characterized in adults. In comparative clinical trials involving adults with type 1 diabetes, insulin detemir, at equivalent glycemic control to NPH insulin, has been associated with risk reductions in hypoglycemia and nocturnal hypoglycemia and reduced variability in fasting plasma glucose (17–19).

Because insulin detemir may offer the advantages of reduced within-subject variability, a protracted and stable action profile, and reduced risk of hypoglycemia, it holds great potential as a basal insulin treatment, particularly for children. This is the first trial to investigate the pharmacokinetic profile of insulin detemir in children and adolescents. An additional purpose of the study was to evaluate, in a comparison with NPH insulin, whether pharmacokinetic profiles in children and adolescents with type 1 diabetes could be considered equivalent to those observed in adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

The trial subjects were 13 children, 10 adolescents, and 11 adults of Caucasian origin with type 1 diabetes of at least 12 months' duration and HbA_{1c} ≤12.0% (Table 1). Subjects were required to be using insulin treatment at least twice daily (total daily dose ≥0.6 IU/kg) and have a BMI of 15–20 kg/m^2, 18–25 kg/m^2, and ≤30 kg/m^2 for children, adolescents, and adults, respectively. Children were in Tanner stage 1. Informed consent was obtained from all patients as well as from the parents or guardians of all children. Patients with evidence of late diabetic complications or any significant disease or condition likely to affect pharmacokinetic or health outcomes were excluded. The trial was carried out in accordance with International Conference of Harmonisation Good Clinical Practice Guidelines (20,21) and was approved by the local ethics committee.

Procedures

Design. This was a single-center, open-label, randomized, crossover trial comprising a screening visit and two dosing/blood sampling visits separated by a washout period of 7–14 days. The patients were given a single dose of either 0.5 units/kg (12 nmol/kg) insulin detemir or 0.5 IU/kg (3 nmol/kg) NPH insulin before breakfast, followed by a 24-h blood sampling period. Patients fasted for 10 h preceding each sampling period and were not to use long- or short-acting insulin for 14 or 8 h, respectively, before each sampling period. Insulin aspart was the only other insulin treatment allowed and was to be used if blood glucose was ≥14 mmol/l in the late postprandial period or during the night. All insulin was given subcutaneously by investigators in the right thigh using a Novopen 3.0 and a NovoFine 30 8-mm needle. Snacks were provided and standardized meals were served for breakfast, lunch, and dinner. Subjects returned to their usual insulin regimens after each 24-h sampling period.

Blood sampling. Serial blood sampling was performed at 30-min intervals during the first 6 h of each dosing visit and thereafter at nominal times (6, 7, 8, 10, 12, 16, 20, and 24 h) during the remaining 18 h. Total serum insulin detemir concentration (both free and bound) was analyzed using a validated specific enzyme-linked immunosorbent assay (ELISA) (lowest level of quantification 15 pmol/l) that does not cross-react with human insulin or aspart. Serum human insulin was analyzed using a DAKO Human Insulin ELISA (22) that does not cross-react with insulin aspart (lowest level of quantification 11 pmol/l). Serum glucose was measured at 12 time points after each administration of the trial product in case of the need to provide carbohydrate snacks.

Pharmacokinetics. The actual time points were used for calculation of the area under the curve (AUC), AUC from zero to infinity [$AUC_{(0-\infty)}$], AUC from 0 to 24 h [$AUC_{(0-24\ h)}$], the maximum concentration measured during the 24 h after dosing (C_{max}), time to maximum concentration (t_{max}), and the mean residence time (MRT). All end points were calculated using noncompartmental techniques. Due to variation in onset of the elimination phase and a very slow decline after reaching C_{max} for some profiles, a

Table 2—*Pharmacokinetic parameters of insulin detemir and NPH insulin for children, adolescents, and adults with type 1 diabetes*

	Age-group		
	6–12 years	13–17 years	18–65 years
Insulin detemir			
n	10	10	9
$AUC_{(0-\infty)}$ (pmol · l^{-1} · min^{-1})	4,078,672 ± 1,789,975	3,373,627 ± 754,187	3,896,543 ± 1,516,217
$AUC_{(0-24h)}$ (pmol · l^{-1} · min^{-1})	3,764,915 ± 1,574,934	3,082,003 ± 607,080	3,382,071 ± 1,419,125
C_{max} (pmol/l)	5,907 ± 3,229	4456 ± 1,073	4,641 ± 2,299
t_{max} (min)	309 ± 137	426 ± 122	483 ± 206
t_{12} (min)	302 ± 100	301 ± 107	425 ± 78
Cl/F (l · min^{-1} · kg^{-1})	3.43 ± 1.36	3.74 ± 0.98	3.41 ± 1.00
MRT (min)	653 ± 162	705 ± 182	827 ± 140
NPH insulin			
n	9	10	7
$AUC_{(0-24h)}$ (pmol · l^{-1} · min^{-1})	411,093 ± 483,066	207,974 ± 153,624	111,941 ± 77,941
C_{max} (pmol/l)	595 ± 594	355 ± 347	149 ± 121
t_{max} (min)	363 ± 247	318 ± 267	480 ± 237

Data are means ± SD.

reliable estimate of the terminal elimination constant could not be determined for human insulin. Consequently, the end points $AUC_{(0-\infty)}$, terminal half-life ($t_{1/2}$), MRT, and Cl/F {apparent clearance [defined as dose/$AUC_{(0-\infty)}$, where dose is calculated in nanomoles]} were only determined for insulin detemir and not after the administration of NPH insulin.

Adverse events. Adverse events were to be recorded regardless of whether related to the trial products. Particular attention was paid to hypoglycemia. A major hypoglycemic episode was defined as one in which the subject was unable to self-treat and when either blood glucose was <2.8 mmol/l (50 mg/dl) or symptoms remitted after intake of food or glucagon/IVglucose. A minor hypoglycemic episode was defined as a blood glucose measurement <2.8 mmol/l (50 mg/dl) that the subject handled without assistance from others. Hematology, biochemistry, and urinalysis tests were performed at the screening and final sampling visits.

Statistical analysis

Sample size calculations showed that nine subjects in each group were sufficient to detect a 20% difference in mean AUC with a power of 80%. To account for dropouts, 10 subjects were recruited to each group. After log-transformation, the pharmacokinetic end points of $AUC_{(0-\infty)}$ as well as $AUC_{(0-24\ h)}$ and C_{max} were analyzed in a one-way ANOVA with age-group as a fixed effect. Pairwise comparisons of children versus adults and adolescents versus adults were also performed for these parameters by estimating the ratio between the age-groups and the corresponding 95% CI using adults as the reference group. Statistical analyses of t_{max} were not made because individual values were widely distributed (between 120 and 960 min) with both insulins, with no apparent relationship to age. For insulin detemir only, t_{max}, $t_{1/2}$, MRT, and Cl/F were presented descriptively. Statistical analyses were performed using SAS version 8.2 and Proc-StatXact for SAS users version 4.01.

RESULTS

Twenty-nine individuals completed the trial. Two adults were withdrawn due to protocol violations (both involving the administration of NPH insulin), and three children withdrew consent during their second visits (two involving NPH insulinand one involving insulin detemir administration). Due to invalid measurements or high baseline human insulin concentrations incompatible with the protocol, data from a further three patients (two adults and one child) were excluded from the NPH insulin analyses. Thus, pharmacokinetic end point assessments were made using data from 10 children, 10 adolescents, and 9 adults for insulin detemir and 9 children, 10 adolescents, and 7 adults for NPH insulin.

Pharmacokinetics

Data regarding pharmacokinetic parameters are summarized in Table 2, and the mean serum concentration–time profiles are shown in Fig. 1. For insulin detemir, analysis of $AUC_{(0-\infty)}$ and C_{max} showed no statistically significant overall age effect (Table 3). This was confirmed by pairwise comparisons of these variables between children and adults and between adolescents and adults.

In the case of NPH insulin, the overall age effect did not reach statistical significance in the ANOVA analysis for $AUC_{(0-24h)}$ ($P = 0.08$) or C_{max} ($P = 0.12$). However, pairwise comparisons for $AUC_{(0-24h)}$ and C_{max} suggested a difference between children and adults for $AUC_{(0-24h)}$ and C_{max} (Table 3). The pairwise comparison between adolescents and adults did not reach statistical significance, but the ratios and CIs were greatly skewed, again suggestive of greater insulin exposure in the younger age-group (Table 3).

The mean pharmacokinetic profiles, shown in Fig. 1, also suggest greater consistency across age-groups for insulin detemir than NPH insulin. An apparent temporary decline in serum levels, seen with both NPH insulin and insulin detemir 2–4 and 4–6 h after injection, respectively, in the children may be attributed to anomalous and missing values for two patients.

Coefficients of variation (CVs) are summarized in Table 4. Insulin detemir was clearly less variable in its pharmacokinetic profile across all three age-groups.

The $t_{1/2}$ for insulin detemir was shorter in children (302 min) and adoles-

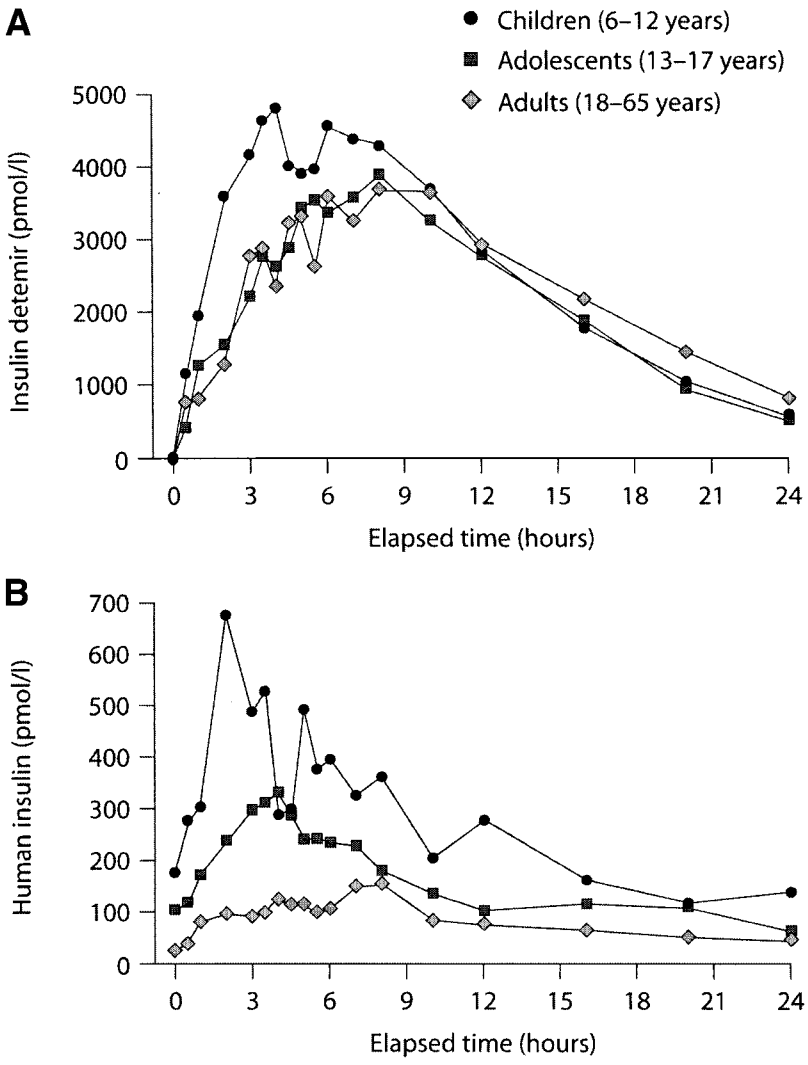

Figure 1—*Mean serum concentration–time profile of insulin detemir and NPH insulin by age-group. A: Insulin detemir. B: NPH insulin.*

cents (301 min) than in adults (425 min). Likewise, MRT was also shorter in children (653 min) and adolescents (705 min) than in adults (827 min), although clearance adjusted for body weight was similar between age-groups for insulin detemir, with means for children, adolescents, and adults of 3.43, 3.74, and 3.41 l · min^{-1} · kg^{-1}, respectively.

Safety

There were no serious adverse events reported during the trial. Approximately 10% of children and adolescents experienced adverse events during treatment with both insulins, but none was considered related to the trial medications. No clinically significant changes in hematology (hemoglobin, white blood cell count, and platelet count), biochemistry (sodium, potassium, creatinine, glucose, total protein, albumin, alanin aminotransferase [ALAT], and alkaline phosphatase), vital signs, or assessments of physical examination were reported (data not shown). No major hypoglycemic episodes were recorded. A total of 45 minor hypoglycemic episodes were reported. Frequencies of these events were similar between the two insulin preparations and were more common in children irrespective of treatment.

CONCLUSIONS — The present study aimed to assess whether the pharmacokinetic profiles of insulin detemir, the novel basal insulin analog, when given to children or adolescents with type 1 diabetes differ from that seen in an adult reference group. For comparative reasons, the pharmacokinetic profiles of NPH insulin in the same three groups were also assessed. The data suggest that insulin detemir is associated with a consistent pharmacokinetic profile across age ranges, while there are indications of an age effect in association with NPH insulin. Although the overall analysis of age effect did not reach statistical significance for NPH insulin [$AUC_{(0-24\ h)}$, $P = 0.08$; C_{max}, $P = 0.12$], data were only available for seven adults, weakening the power of the evaluations. Despite this, significant differences were found in pairwise comparisons between children and adults. Age effects have been shown previously for human insulin and insulin aspart, however, with lower concentrations in the younger age-group (23). These age effects are still poorly understood, and factors affecting absorption, degradation, and clearance have to be considered. For example, the clearance of human insulin is known to vary with age in young subjects with type 1 diabetes and is influenced by circulating growth hormone concentrations (24).

Specifically, the mean time–concentration curve and pharmacokinetic profile of NPH insulin progressively departed from those of an ideal basal insulin in younger age ranges with evidence of progressively more rapid absorption toward an early peak effect (Fig. 1). This property of NPH insulin has been shown to lead to high free insulin levels in children at night that are associated with a higher risk for nocturnal hypoglycemia (25). Such an effect was greatly attenuated with insulin detemir and was not statistically significant. This is a welcome finding suggesting that in juvenile patients insulin detemir could have clinical advantages over NPH insulin, which is widely used as basal insulin in children (26). Moreover, when used in children and adolescents, insulin detemir could be titrated using similar guidelines to adults, potentially offering more predictability than NPH insulin in this respect. Furthermore, lower CVs imply that the pharmacokinetic profile of insulin detemir is more consistent between subjects within each age-group compared with NPH insulin.

The availability of a protracted basal insulin analog that does not differ significantly in its pharmacokinetic profile across ages and which has reduced overall

Table 3—*Analysis of effect of age on pharmacokinetic parameters of insulin detemir and NPH insulin for children, adolescents, and adults with type 1 diabetes*

	$AUC_{(0-\infty)}$ (μmol/l) min	$AUC_{(0-24h)}$ (μmol/l min)	C_{max} (pmol/l)
Insulin detemir			
Overall *P* value*	0.65	0.61	0.41
Children vs. adults†	1.02 (0.74–1.41)	1.10 (0.81–1.50)	1.24 (0.86–1.79)
Adolescents vs. adults†	0.89 (0.65–1.23)	0.95 (0.70–1.30)	1.02 (0.71–1.47)
NPH insulin			
Overall *P* value*	—	0.08	0.12
Children vs. adults†	—	2.92 (1.14–7.44)	3.24 (1.06–9.95)
Adolescents vs. adults†	—	1.93 (0.77–4.83)	2.07 (0.69–6.20)

Data are estimated ratio (95% CI). *For overall differences between the three age-groups (ANOVA); †pairwise comparisons versus adult cohort.

variability is clinically welcome, especially perhaps for younger patients, who are at greater risk of hypoglycemia (including nocturnal episodes) than adults (4,27–31). Children are known to be particularly vulnerable to variable absorption rates due to their unpredictable exercise patterns, tendency for low subcutaneous adiposity, poor injection technique, and the presence of lipohypertrophy (32–34).

This relative reduction in between-subject variability seen in this study versus NPH insulin complements findings of decreased within-subject variability in previous comparative trials (17,19,35). Insulin detemir's relative reduction in overall pharmacokinetic variability across (and within) age ranges may relate to the fact that, unlike other basal insulins such as NPH insulin and insulin glargine, it remains in solution after injection rather than forming a precipitate. It therefore forms a depot with a larger surface area, which is likely to result in a more stable absorption pattern (8). This factor, combined with albumin binding, may slow and stabilize absorption rates, compensating for structural differences between individuals' subcutaneous connective tissue.

In summary, this study suggests that insulin detemir is suitable for use in children, adolescents, and adults as a basal insulin, and that it may have clinical advantages, such as more predictable hypoglycemic responses, over NPH insulin as a result of reduced pharmacokinetic variability across age ranges and between individuals. Findings in larger treatment trials are needed to confirm these implications.

Table 4—*Between-subject CV of pharmacokinetic parameters for insulin detemir and NPH insulin*

	Insulin detemir	NPH insulin
$AUC_{(0-24h)}$		
Children	42	118
Adolescents	20	74
Adults	42	70
C_{max}		
Children	55	100
Adolescents	24	98
Adults	50	81
t_{max}		
Children	44	68
Adolescents	29	84
Adults	43	49

Data are percent.

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