Original Article

Insulin degludec's ultra-long pharmacokinetic properties observed in adults are retained in children and adolescents with type 1 diabetes

Insulin degludec (IDeg) is a basal insulin with an ultra-long pharmacokinetic profile in adults that at steady-state produces remarkably flat and stable insulin levels; however, no studies have yet reported on the pharmacokinetic properties of IDeg in subjects younger than 18 years of age. This was a single-centre, randomised, single-dose, double-blind, two-period crossover trial conducted in children (6–11 years), adolescents (12–17 years), and adults (18–65 years) with type 1 diabetes. Subjects received a single subcutaneous dose of 0.4 U/kg IDeg or insulin glargine (IGlar), respectively, on two separate dosing visits, with pharmacokinetic blood sampling up to 72-h postdose. A total of 37 subjects (12 children, 13 adolescents, and 12 adults) completed the trial. Total exposure of IDeg after a single dose ($AUC_{IDeg,0-\infty,SD}$) was higher in children compared to adults [estimated ratio children/adults 1.48 (95% confidence interval, CI: 0.98; 2.24)] and in adolescents compared to adults [estimated ratio adolescents/adults 1.33 (95% CI: 1.08; 1.64)]; however, the difference was only statistically significant for the latter comparison. No statistically significant difference in maximum concentration of IDeg ($C_{max,IDeg,SD}$) was observed. Estimated ratios for $C_{max,IDeg,SD}$ were (children/adults) 1.20 (95% CI: 0.90; 1.60) and (adolescents/adults) 1.23 (95% CI: 1.00; 1.51). Simulated mean steady state pharmacokinetic profiles supported a flat and stable IDeg exposure across a 24-h dosing interval. IDeg was detectable in serum for at least 72 h (end of blood sampling period) in all subjects following single dose. In conclusion, the ultra-long pharmacokinetic properties of IDeg observed in adults are preserved in children and adolescents with type 1 diabetes.

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The incidence of type 1 diabetes in children is increasing worldwide (1, 2), a trend that is predicted to continue in coming years (3). While intensive insulin therapy has become a mainstay of treatment and an important way to reduce long-term complications (4), adherence remains a barrier to optimal glycaemic

control in children with type 1 diabetes (5), particularly considering the erratic daily schedules and eating habits of school-age children. Data collected from insulin pump users suggest that missed boluses are common and can adversely affect overall glycated haemoglobin (HbA1c) levels (6). Treatment in children and adolescents is further complicated by the risk of hypoglycaemia, requiring monitoring and adjustment of basal and bolus insulin doses with variation in levels of physical activity (7) or diet (8). Glycaemic control may also be compromised by suboptimal dosing due to fear of hypoglycaemia among parents and children (9).

Insulin degludec (IDeg, Novo Nordisk A/S, Bagsvaerd, Denmark) is a new generation basal insulin with an ultra-long duration of action, developed for once-daily administration in all patients. Upon subcutaneous (SC) administration, IDeg forms a SC depot of long chains of multi-hexamers, from which monomers are slowly and continuously absorbed into the circulation (10, 11). This unique mechanism provides a flat and stable action profile at steady state with an ultra-long duration of action beyond 42 h in adults (12–14), suggesting that delayed injections may not affect glycaemic control to the same degree as with current basal insulins (15, 16). Furthermore, results from the BEGIN™ (Novo Nordisk A/S) clinical trial programme show significantly lower rates of nocturnal hypoglycaemia in adults with type 1 diabetes compared to insulin glargine (IGlar; Lantus®, Sanofi, Paris, France) (17). These characteristics of IDeg could allow greater accommodation of insulin therapy to the varying lifestyles observed in children and adolescents.

The aim of this study, the first evaluating IDeg in children and adolescents, was to determine the pharmacokinetic properties, safety, and tolerability of IDeg after a single dose in children and adolescents compared to adults, all with type 1 diabetes.

Methods

Study populations

Eligible participants had been receiving multiple daily insulin injections or continuous subcutaneous insulin infusion (CSII) for the treatment of type 1 diabetes for ≥12 months, with a total daily insulin requirement of 0.6–1.2 U/kg/d and HbA1c levels ≤10.0% (≤86 mmol/mol) at screening. The age limits for the study groups were 6–11 years (children); 12–17 years (adolescents), and 18–65 years (adults), with body mass index (BMI) limits of 15.0–20.0; 18.0–28.0, and ≤30.0 kg/m², respectively. Children <6 years old were not eligible for participation (due to the burdens associated with hospital stay and frequent blood sampling) nor were subjects with underlying medical conditions or medications that could, in the opinion of the investigator, interfere

with insulin pharmacokinetics. Participants had not received any long-acting insulin [IGlar or insulin detemir (Levemir®, Novo Nordisk A/S)] less than 48 h prior to dosing, and had not received any intermediate-acting insulin [e.g. neutral protamine Hagedorn (NPH) insulin] less than 12 h prior to dosing. Subjects could not participate if they had experienced an episode of severe hypoglycaemia within the 24 h prior to dosing.

Study design

This was a single-centre (Kinder- und Jugendkrankenhaus auf der Bult, Diabetes-Zentrum für Kinder und Jugendliche, Hannover, Germany), randomised, single-dose, double-blind, two-period crossover trial conducted in children, adolescents, and adults with type 1 diabetes (ClinicalTrials.gov number: NCT01030926). The protocol, protocol amendment, consent form, and subject information sheet were reviewed and approved by appropriate authorities and ethics committee according to local regulations, and by an appropriately constituted review board, prior to trial initiation. This study was performed in accordance with the Declaration of Helsinki and its amendments, and Good Clinical Practice as defined by the International Conference on Harmonisation, as in force at trial initiation. All subjects (and their legal guardians for children and adolescents) were informed of the risks and benefits of the trial and that they could withdraw from the trial at any time, for any reason. Consent was obtained in writing before any trial-related activities, and the investigator retained the consent forms.

Interventions and pharmacokinetic sampling

Following screening, each subject was randomly allocated to receive one single dose of IDeg at Visit 2 and IGlar at Visit 3, or vice versa, with a washout period of 7–21 days between administrations (Fig. 1). IDeg and IGlar were administered SC into a lifted skinfold on the anterior surface of the thigh as a single dose of 0.4 U/kg using a syringe and needle. IGlar was included primarily as a control. In case differences between age groups were observed for IDeg, it would be possible to investigate the corresponding differences between age groups for IGlar. At each dosing visit, subjects stayed in hospital under observation for 48 h after dosing. Blood samples for pharmacokinetic and blood glucose analyses were drawn at 0 h (predose) then frequently over 48 h (while in hospital) before returning for a final blood sample at 72 h postdosing. Bolus insulin (insulin aspart, NovoRapid®, Novo Nordisk A/S) was administered under investigator supervision to maintain glycaemic control during dosing visits. Patients and study personnel were blinded to the medication provided.
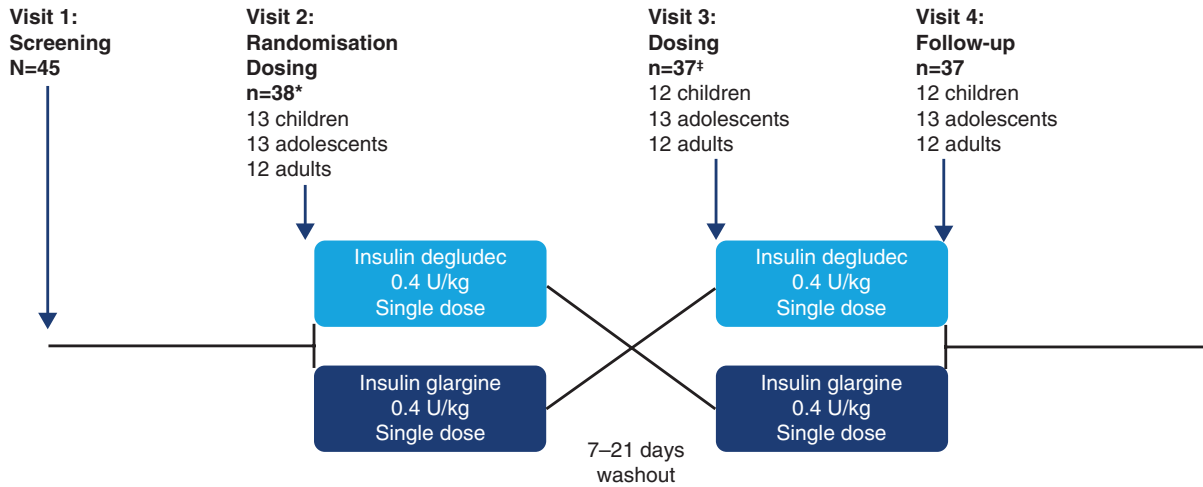
Fig. 1. Patient disposition. Asterisk (*): 39 subjects were randomised; however, one adult withdrew consent after being randomised but before being exposed to drug. Dagger (†): One child was withdrawn after Visit 2 because of difficult venous conditions (no pharmacokinetic data were obtained).

IDeg and IGlar analysis

Serum IDeg concentration was measured using a validated IDeg-specific sandwich enzyme-linked immunosorbent assay (ELISA), whereas serum IGlar concentration was measured using a validated IGlar-specific luminescent oxygen channelling immunoassay (LOCI) (18).

Data and statistical analyses

The primary objective was to compare the total exposure of IDeg between children, adolescents, and adults with type 1 diabetes following a single dose. The primary endpoint was the area under the serum IDeg concentration curve ($AUC_{IDeg,0-\infty,SD}$), and was calculated as the sum of two areas; namely the area under the curve from zero to last quantifiable concentration at time t_z, and the area from t_z to infinity. Log-transformed $AUC_{IDeg,0-\infty,SD}$ was analysed using an analysis of variance (ANOVA) method with age group (children/adolescents/adults) and treatment period (period 1/period 2) as factors, with different error terms for each age group.

Secondary objectives included comparison of pharmacokinetic properties (other than total exposure) of IDeg across age groups, comparison of pharmacokinetic properties of IGlar across age groups, as well as safety and tolerability. Secondary pharmacokinetic endpoints included maximum observed serum IDeg concentration ($C_{max,IDeg,SD}$), area under the serum IGlar concentration curve ($AUC_{IGlar,0-\infty,SD}$), and maximum observed serum IGlar concentration ($C_{max,IGlar,SD}$). The log-transformed secondary endpoints were analysed using the same model as for the primary endpoint. Safety endpoints included adverse events (AEs) including local injection site reactions, laboratory safety variables, physical examination, vital signs, and hypoglycaemic episodes. Hypoglycaemic episodes were defined as 'confirmed' when they were either classified as 'severe' as defined by the American Diabetes Association (19) or verified by a plasma glucose concentration <3.1 mmol/L (56 mg/dL). Safety endpoints were summarised using descriptive statistics.

Pharmacokinetic modelling

To simulate the mean steady state pharmacokinetic profile of IDeg from this single-dose study, a population pharmacokinetic model was used. The model consisted of an absorption part with a depot compartment, a delay compartment, an absorption rate parameter, and a delay rate parameter; and a disposition part with one compartment, a clearance parameter, and a volume of distribution parameter. The parameters of the model were estimated in a population pharmacokinetic setting using a non-linear mixed-effects approach, which allowed individual sets of the four parameters for each of the subjects included in the trial to be obtained. Values of the absorption rate parameter were subsequently calibrated based on additional information from the comprehensive clinical pharmacology programme with IDeg (the same calibration factor was applied for all subjects). Using the individual parameters, a simulation of multiple once-daily dosing was carried out to obtain a mean steady state profile. More specifically, multiple once-daily dosing for 6 days at a dose level of 0.4 U/kg was simulated by extrapolating the profile for each of the subjects and subsequently calculating the mean of the profiles on Day 6.

Table 1. Subject characteristics

Characteristic	Children	Adolescents	Adults
Subjects, n	12	13	12
Age, years	10.3 (1.1)	14.3 (1.6)	25.6 (11.9)
Sex, n (%)			
Female	5 (42%)	7 (54%)	5 (42%)
Male	7 (58%)	6 (46%)	7 (58%)
Height, m	1.51 (0.08)	1.69 (0.08)	1.76 (0.11)
Weight, kg	42.3 (7.2)	61.6 (7.1)	78.0 (9.2)
BMI SD score (20) median (SD)	0.49 (0.59)	0.54 (0.73)	1.12 (0.77)
Duration of diabetes, years	5.1 (2.4)	5.9 (4.1)	13.8 (8.3)
HbA1c, %	7.7 (0.8)	7.7 (0.5)	7.6 (1.0)
HbA1c, mmol/mol*	60.7 (8.7)	60.7 (5.5)	59.6 (10.9)

Values are mean (SD) unless otherwise indicated.
BMI, body mass index; HbA1c, glycated haemoglobin; SD, standard deviation.
*IFCC-HbA1c (mmol/mol) = [DCCT-HbA1c (%) − 2.15] × 10.929

Results

Subjects

Of 45 subjects screened, 39 were randomised and 38 (13 children, 13 adolescents, and 12 adults) were exposed to drug and thus included in the safety data set. One child was withdrawn after Visit 2 because of difficulty in drawing blood (no pharmacokinetic data were obtained). The remaining 37 subjects (12 children, 13 adolescents, and 12 adults) completed the trial and were included in the pharmacokinetic data set (Fig. 1). All subjects were Caucasian, with an equal distribution of males and females (close to 50/50) in each age group (Table 1). Mean [standard deviation (SD)] age was 10.3 (1.1), 14.3 (1.6), and 25.6 (11.9) yr among children, adolescents, and adults, respectively.

Pharmacokinetics

Mean serum IDeg concentration–time profiles in children, adolescents, and adults expressed as a percentage of the maximum mean concentration among the three age groups are shown in Fig. 2. Serum IDeg was still detectable in all subjects at 72 h after dosing (end of observation period). Total exposure ($AUC_{IDeg,0-\infty,SD}$) of IDeg after single-dose administration was higher in children [145 891 pmol*h/L, coefficient of variation (CV): 73%] compared to adults [98 594 pmol*h/L (CV: 21%)], and in adolescents [130 713 pmol*h/L (CV: 30%)] compared to adults, however the difference was only statistically significant for adolescents vs. adults (Table 2). The maximum serum concentration of IDeg ($C_{max,IDeg,SD}$) was higher in children [3350 pmol/L (CV: 51%)] compared to adults [2792 pmol/L (CV: 17%)], and in adolescents [3422 pmol/L (CV: 33%)] compared to adults, however none of these differences were statistically significant (Table 2).
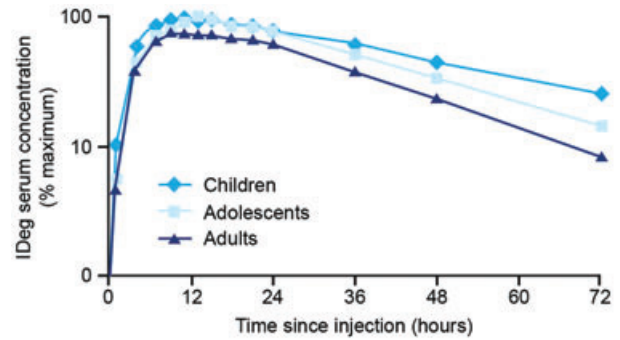

Fig. 2. Mean serum insulin degludec concentrations over 72 h after a single dose in children, adolescents and adults (expressed on a logarithmic scale as a percentage of the maximum mean concentration among the three age groups).

Serum IGlar concentrations fell below the lower limit of quantification for the majority of subjects after 36–48 h. As with IDeg, the total exposure of IGlar after single-dose administration ($AUC_{IGlar,0-\infty,SD}$) was higher in children than in adults, although the difference was not statistically significant (see Table 2). $AUC_{IGlar,0-\infty,SD}$ was comparable between adolescents and adults. Likewise, $C_{max,IGlar,SD}$ was similar between children and adults and between adolescents and adults (see Table 2).

A population pharmacokinetic model was used to predict mean steady state IDeg pharmacokinetic profiles for once-daily 0.4 U/kg SC administration (Fig. 3; Table 3). The shapes of the pharmacokinetic profiles of IDeg for children and adolescents were similar to the shape of the adult profile (Fig. 3), with an even distribution of exposure across a 24-h dosing interval. Total exposure and maximum concentration of IDeg at steady state were higher in children and adolescents compared to adults, with the difference only being statistically significant for children (Table 3).

Safety

In total, 10 AEs were reported among seven subjects following IDeg treatment (three children, three adolescents, and one adult), of which 5 AEs (two cases of headache, one case of upper abdominal pain, one case of nausea, and one case of moderate oropharyngeal pain) in three patients were considered to have a possible or probable relationship with IDeg treatment. All but one AE were mild or moderate in severity. A single severe adverse event (SAE) was reported in which a female adolescent presented with 21 confirmed treatment-emergent hypoglycaemic episodes during the course of the study (7 following IDeg treatment and 14 following IGlar treatment). The subject had not presented with factors relating to hypoglycaemic unawareness, and no facticial disorder was made known to the investigators. The electronic readout of the subject's insulin pump

Table 2. Pairwise comparison of insulin total exposure and maximum concentration in children and adolescents vs. adults after a single dose

| | Ratio (95% CI) | | | |
| | IDeg | | IGlar | |
	$AUC_{0-\infty,SD}$	$C_{max,SD}$	$AUC_{0-\infty,SD}$	$C_{max,SD}$
Children vs. adults	1.48 (0.98; 2.24)	1.20 (0.90; 1.60)	1.27 (0.90; 1.79)	1.00 (0.73; 1.37)
Adolescents vs. adults	1.33 (1.08; 1.64)*	1.23 (1.00; 1.51)	1.08 (0.77; 1.52)	0.90 (0.66; 1.22)

$AUC_{0-\infty,SD}$, area under the serum insulin concentration–time curve from zero to infinity after single dose; CI, confidence interval; $C_{max,SD}$, maximum observed serum insulin concentration after a single dose; IDeg, Insulin degludec; IGlar, insulin glargine.
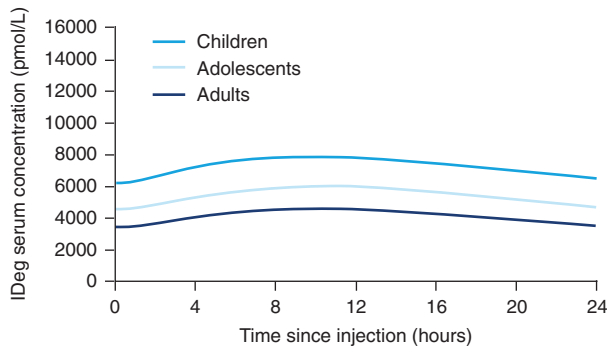*Difference is statistically significant.

Fig. 3. Simulated mean serum insulin degludec concentration–time profiles over a 24-h dosing interval at steady state in children, adolescents and adults (see section Methods for details).

Table 3. Pairwise comparison of insulin degludec total exposure and maximum concentration in children and adolescents vs. adults at steady state based on simulation

| | Ratio (95% CI) | |
	$AUC_{IDeg,\tau,SS}$	$C_{max,IDeg,SS}$
Children vs. adults	1.52 (1.08; 2.12)*	1.50 (1.08; 2.06)*
Adolescents vs. adults	1.29 (0.94; 1.78)	1.28 (0.94; 1.74)

$AUC_{IDeg,\tau,SS}$, area under the serum insulin degludec (IDeg) concentration–time curve during a dosing interval at steady state; CI, confidence interval; $C_{max,IDeg,SS}$, maximum observed serum IDeg concentration at steady state.
*Difference is statistically significant.

showed additional bolus doses that had not been recorded. This SAE was recorded as 'suspected recurrent hypoglycaemia factitia', and considered by the investigators unlikely to be related to IDeg.

A total of five AEs were reported in five subjects following IGlar treatment, of which all were mild or moderate in severity and one considered to have a possible or probable relationship with IGlar. No apparent differences were observed in the pattern of AEs for IDeg compared to IGlar.

Seventy-five confirmed treatment-emergent hypoglycaemic episodes were reported for IDeg by 21 subjects (68 hypoglycaemic episodes in 20 subjects if

excluding the subject with an SAE of suspected recurrent hypoglycaemia factitia; see above). No differences were observed in the number of treatment-emergent hypoglycaemic episodes across age groups and no severe hypoglycaemic episodes were reported. This compared with 101 confirmed hypoglycaemic episodes for IGlar reported in 21 subjects (87 hypoglycaemic episodes in 20 subjects if excluding the subject with an SAE of suspected recurrent hypoglycaemia factitia; see above), also distributed evenly across age groups, and without any reported severe hypoglycaemic episodes.

There were no clinically significant changes observed in laboratory parameters, vital signs or physical examination for either treatment.

Discussion

This study characterised the pharmacokinetic properties and safety profile of IDeg in children, adolescents, and adults with type 1 diabetes. Notably, the ultra-long pharmacokinetic profile of IDeg observed in adults was preserved in both children and adolescents following a single dose. Differences in IDeg total exposure and maximum concentration were observed between populations, some of which reached statistical significance. Simulations supported that the shape of the steady state pharmacokinetic profile of IDeg, with flat and stable IDeg exposure across a 24-h dosing interval, is preserved in children and adolescents. IDeg was well tolerated in all age groups in this study.

In this study, observation ended at 72 h after a single dose, at which time point all subjects still had detectable IDeg serum concentration. Of particular note was the presence of relatively high serum IDeg concentrations demonstrated 42 h after administration for all three age groups. The ultra-long pharmacokinetic properties of IDeg therefore appear to be preserved in children and adolescents, suggesting that the duration of action would also be prolonged in these age groups. Furthermore, simulated mean steady state pharmacokinetic profiles supported that

the flat and stable IDeg exposure, as also shown in other studies (13, 14), are preserved in children and adolescents. While some differences were observed in total exposure and maximum concentration between populations, this is unlikely to be clinically relevant, as IDeg dose should be adjusted according to individual needs based on glycaemic response as with all other insulin products. This is particularly so in children and adolescents as age-dependent differences in insulin exposure are not uncommon, especially during puberty. Thus, differences between age groups seem more likely related to the biology of insulin absorption/disappearance than the physical chemistry of the insulin. Indeed, in a similar study conducted in subjects receiving insulin detemir, $AUC_{0-\infty}$ and C_{max} also tended to be higher in children compared to adults, however this difference was not significantly different (21).

Adolescence is known to be the most difficult time to achieve good glycaemic control in paediatric diabetes (22). Irregular lifestyles and sleeping patterns make it particularly difficult to adhere to a regular pattern of insulin injections. Thus, the possibility of dosing IDeg at any time of day, and at different times from day to day when needed without compromising efficacy or risk of hypoglycemia (15), may be beneficial in paediatric diabetes. This however needs to be assessed through experience.

In this study, the ultra-long pharmacokinetic properties of IDeg were demonstrated to be preserved in children and adolescents. Further studies are warranted to examine the clinical effects of IDeg in children and adolescents, particularly regarding the flat and stable glucose-lowering effect, the low within-subject variability, and the lower hypoglycaemia rates observed in the adult population (12, 17). A larger between-subject variability in exposure was observed in adolescents and children compared to adults. However, as insulin is individually titrated, this observation on between-subject variability is less clinically important as compared to the within-subject variability. Children are particularly vulnerable to variable absorption rates due to their unpredictable lifestyle patterns, poor injection technique (23), and lipohypertrophy (24). As a result, any significant reduction in within-subject variability in this population has the potential to improve current treatment standards. In the case of insulin detemir, another basal insulin, similarly lower within-subject variability compared to IGlar has been documented in both adults (25) and children/adolescents (26). With respect to IDeg, results in the adult population indicate that IDeg has four times lower within-subject variability in glucose-lowering effect compared to IGlar based on a more consistent pharmacokinetic profile for IDeg (12, 14). Since the mechanism of protraction of

IDeg is anticipated to be the same in adults and children/adolescents, as also indicated by comparable pharmacokinetic properties, we would anticipate that within-subject variability also will be low for IDeg in children and adolescents.

In conclusion, the ultra-long pharmacokinetic profile of IDeg seen in adults is preserved in children and adolescents with type 1 diabetes. While careful titration of insulin should always be based on individual needs, and particularly so in children, the present findings suggest that the benefits associated with the ultra-long pharmacokinetic properties of IDeg may also pertain to children and adolescents with type 1 diabetes. More specifically, the ultra-long duration of action of IDeg could prove relevant in the treatment of paediatric patients through reducing the impact of erratic dosing schedules and mistimed basal doses. Paediatric studies investigating the potential clinical benefits of IDeg are therefore warranted.

Acknowledgements

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