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Original article

Morning administration of 0.4 U/kg/day insulin glargine 300 U/mL provides less fluctuating 24-hour pharmacodynamics and more even pharmacokinetic profiles compared with insulin degludec 100 U/mL in type 1 diabetes

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ABSTRACT

Aim. – To compare steady state pharmacodynamic and pharmacokinetic profiles of insulin glargine 300 U/mL (Gla-300) with insulin degludec 100 U/mL (Deg-100) in people with type 1 diabetes.
Methods. – This single-centre, randomized, double-blind crossover euglycaemic clamp study included two parallel cohorts with fixed once-daily morning dose regimens. For both insulins participants received 0.4 ($n = 24$) or 0.6 U/kg/day ($n = 24$), before breakfast, for 8 days prior to the clamp. The main endpoint was within-day variability (fluctuation) of the smoothed glucose infusion rate (GIR) over 24 hours (GIR-smFL$_{0–24}$).
Results. – Gla-300 provided 20% less fluctuation of steady state glucose infusion rate profiles than Deg-100 over 24 hours at 0.4 U/kg/day (GIR-smFL$_{0–24}$ treatment ratio 0.80 [90% confidence interval: 0.66 to 0.96], $P = 0.047$), while at the dose of 0.6 U/kg/day the difference between insulins was not statistically significant (treatment ratio 0.96 [0.83 to 1.11], $P = 0.603$). Serum insulin concentrations appeared more evenly distributed with both dose levels of Gla-300 versus the same doses of Deg-100, as assessed by relative 6-hour fractions of the area under the curve within 24 hours. Both insulins provided exposure and activity until 30 hours (end of clamp).
Conclusion. – Gla-300 provides less fluctuating steady state pharmacodynamic profiles (i.e. lower within-day variability) and more evenly distributed pharmacokinetic profiles, compared with Deg-100 in a once-daily morning dosing regimen of 0.4 U/kg/day.

Introduction

The key component of the management strategy for people with type 1 diabetes (T1DM) and some with type 2 diabetes (T2DM) is basal and prandial insulin replacement. Although subcutaneous (SC) insulin replacement cannot fully mimic the physiology of endogenous insulin secretion [1], advances have been made over the last two decades, particularly with long-acting

Abbreviations: GIR-AUC$_{0–24}$, area under the GIR over time curve; GIR-smFL$_{0–24}$, fluctuation of the smoothed glucose infusion rate; LOESS, locally weighted regression in smoothing scatterplots; MAGE, mean amplitude of glycaemic excursions.

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basal insulin analogues that now exhibit flatter pharmacokinetic (PK) and pharmacodynamic (PD) profiles in a once-daily dosing regimen [2]. Smaller fluctuations (within-day variability) in PD activity, resulting from lower excursions of basal insulin plasma concentrations over the dosing interval, may better reproduce the physiology of basal insulin secretion in the fasting and inter-prandial state [1] and reduce hypoglycaemia risk.

Insulin glargine 300 U/mL (Gla-300) and insulin degludec 100 U/mL (Deg-100) are long-acting basal insulin products, both shown to have prolonged and more stable PK and PD profiles when compared with insulin glargine 100 U/mL (Gla-100) [3,4]. In phase 3 clinical treat-to-target trials, both Gla-300 and Deg-100 have been shown to be non-inferior to Gla-100 in terms of HbA_{1c} reduction, while resulting in less hypoglycaemia [5–7].

The aim of the present crossover study was to compare the PD and PK profiles of the same dose of Gla-300 and Deg-100 given in the morning, at two different dose levels at steady state, by using the euglycaemic clamp technique in people with T1DM.

Materials and methods

Participants

Males and females aged 18–64 years with a duration of T1DM > 1 year on a stable insulin regimen with total daily insulin dose < 1.2 U/kg were included. Participants were required to have a body mass index (BMI) between 18 and 30 kg/m^2, fasting C-peptide < 0.30 nmol/L, and $HbA_{1c} \leq 9.0\%$ (≤ 75 mmol/mol). Exclusion criteria included the presence or history of clinically relevant disease (other than T1DM), more than one episode of severe hypoglycaemia during the past 6 months, pregnancy, breast-feeding, and smoking more than 5 cigarettes or equivalent per day.

Study design and treatment

This single-centre, randomized, double-blind, two-treatment, two-period, two-sequence crossover euglycaemic clamp study (EudraCT Number 2015-004843-38) included two cohorts that each evaluated a different dose level of daily basal insulin (cohort 1, 0.4 U/kg/day [$n = 24$]; cohort 2, 0.6 U/kg/day [$n = 24$]) (Fig. S1; see supplementary data associated with this article online). Participants received treatment in the morning over 8 days with Gla-300 in the first treatment period and Deg-100 in the second treatment period, or vice versa (as assigned per randomization). There was a washout period of 8–26 days between treatment periods, during which participants used their pre-study insulin treatment.

After having washed out all prior basal and intermediate insulin products (washout of 72 hours for ultra-long-acting insulin products, 48 hours for long-acting insulin products, and 24 hours for intermediate-acting insulin products; participants taking short-acting insulin via an SC pump [continuous SC insulin infusion] discontinued their pump at least 30 minutes before the first administration of study medication), the first two doses of study medication were given in an initial in-house period in the mornings on days 1 and 2 to enable an immediate intervention by the medical personnel on-site in case of hypoglycaemia. This was followed by ambulatory on-site visits on days 3–7 in the mornings, during which further basal insulin doses were given by medical personnel, and a final in-house period from day 7 (evening) until day 9 (afternoon) during which the final 8th dose was given on day 8 in the morning and the clamp was initiated. On days 1–7 participants took variable doses of prandial insulin (insulin glulisine, administered in disposable pens for SC injection) at mealtimes as needed, in addition to the fixed daily basal insulin doses. The basal insulin dose on day 8 of each treatment period was given in fasting condition at approximately 08:00 h and followed by a 30-hour euglycaemic glucose clamp. Each treatment was administered subcutaneously in the periumbilical region with daily rotating change of the abdominal quadrants, as a single daily dose, in the mornings at approximately 08:00 h in the research unit by medically trained staff.

The glucose clamp setting was started during the night between days 7 and 8, approximately 8 hours before the last scheduled dosing of study treatment, to stabilize participants' blood glucose (BG) at the euglycaemic target level by the time of dosing (euglycaemia titration period). At this time (around midnight), participants were connected to the clamp device (ClampArt®, Profil, Neuss, Germany [8]). The last meal before the fasting period of the clamp procedure was dinner, given at approximately 7 pm on day 7. At this time, the last dose of prandial insulin was injected. Dinner had to be finished by 20:00 h (12 hours before dosing). During the euglycaemia titration period, participants received a variable intravenous infusion of insulin glulisine (a solution with 15 U insulin glulisine [100 U/mL] in 49 mL saline to which 1 mL of the participant's own blood was added to prevent insulin adhesion) and/or a variable glucose infusion (20%), to achieve and stabilize the BG target level of 5.5 mmol/L (100 mg/dL) ± 20%. The BG target level had to be stable within this range for at least 1 hour prior to dosing and the insulin glulisine infusion had to be discontinued at least 20 minutes before administration of study treatment in the morning on day 8. The euglycaemic clamp was then performed for up to 30 hours from dosing on day 8 with automated adaptations of the glucose infusion rate (GIR) every minute, but was stopped earlier if BG consistently exceeded 11.1 mmol/L (200 mg/dL) for 30 minutes in the absence of intravenous glucose infusion. After the end of the clamp, the participants were served a meal and resumed their pre-study insulin regimen. The study was performed in compliance with Good Clinical Practice, the Helsinki Declaration and local regulations. The protocol was approved by the Ethics Committee of the Regional Medical Council and The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM), and all participants provided written informed consent.

Pharmacodynamic and pharmacokinetic assessments

The main PD endpoint in this study was the fluctuation (within-day variability) of the smoothed GIR curve over a 24-hour dosing period in steady state (GIR-$smFL_{0-24}$) (Fig. S2; see supplementary data associated with this article online). For this endpoint, the area of the individual smoothed GIR above and below the individual average GIR line is calculated, providing the mean amplitude of GIR fluctuations around the average GIR over 24 hours. This measure of within-day variability of PD activity in a euglycaemic clamp has been previously used to compare the within-day variability of basal insulins [4]. Other PD endpoints included area under the body weight standardized GIR curve within 24 hours (GIR-AUC_{0-24}), relative 6-hour fractions of GIR-AUC_{0-24}, maximum smoothed GIR (GIR_{max}), time to 50% of GIR-AUC_{0-24} ($T_{50\%}$-GIR-AUC_{0-24}), and duration of euglycaemia (defined as the time smoothed BG remained ≤ 5.8 mmol/L [≤ 105 mg/dL]).

PK endpoints of the study included area under the serum insulin concentration (INS) curves within 24 hours (INS-AUC_{0-24}), relative 6-hour fractions of INS-AUC_{0-24}, time to 50% of INS-AUC_{0-24} ($T_{50\%}$-INS-AUC_{0-24}), maximum INS (INS-C_{max}), time to INS-C_{max} (T_{max}), swing degree of INS fluctuation ($[C_{max} - C_{min}]/C_{min}$), and relative degree of fluctuation ($[C_{max} - C_{min}]/C_{av}$).

INS was determined using validated radioimmunoassays with a lower limit of quantification of 5.02 μU/mL for insulin glargine and 12 μU/mL for insulin degludec. As these assays are non-specific,

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