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Original research

Reduction of glycemic variability with Degludec insulin in patients with unstable diabetes

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SUMMARY

Introduction: Degludec (IDeg) is an ultralong-acting insulin, with stable pharmacodynamic profile which leads to lower fluctuations in glucose levels. The effect of IDeg has not been specifically assessed in patients with unstable diabetes, defined as increased glycemic variability (GV).

Methods: A prospective before-after pilot study was conducted, including patients managed at Hospital Universitario San Ignacio in Bogotá, Colombia. The impact of the switch from a Glargine or Detemir insulin to a basal insulin regimen with IDeg for 12 weeks on GV measured by continuous glucose monitoring, on A1c levels, and on the incidence of episodes of global and nocturnal hypoglycemia was assessed in a group of patients with (coefficient of variation $> 34\%$) or without increased basal GV using a Generalised Estimating Equation (GEE) analysis.

Results: 60 patients with basal bolus therapy and history of hypoglycemia were included. 18 patients had High GV (HGV). In this group a significant reduction of 11.1% of CV (95% CI: 6.3, 15.9, $p = 0.01$) was found. GEE analysis confirmed a higher impact over time on patients with HGV ($p < 0.001$). The percentage of patients with at least 1 episode of hypoglycemia decreased from 66.6% to 22.2% ($p = 0.02$) and from 37.14% to 5.71% ($p < 0.01$) for global and nocturnal hypoglycemia, respectively. Changes were not significant in patients with low GV. A reduction of A1c was observed in both groups ($p < 0.001$).

Conclusions: The results suggest that treatment with IDeg reduces GV, A1c levels and the incidence of global and nocturnal hypoglycemia events in patients with HGV, but not in patients with low GV.

Introduction

Hypoglycemia events are a risk factor for cardiovascular events [1] and mortality in patients with diabetes mellitus (DM). Occurrence of hypoglycemia episodes is a limiting factor for achieving an adequate metabolic control in diabetes mellitus (DM) patients treated with

Abbreviations: DM1, Type 1 diabetes; DM2, Type 2 diabetes; CGM, Continuos glucose monitoring; TDD, total daily insulin dose; BMI, Body mass index; IQR, interquartile range; SD, Standard deviation; A1c, Glycated hemoglobin; CV, coefficient of variation; MAG, mean absolute glucose change; MAGE, mean amplitude of glucose excursion; CONGA, continuous overall net glycemic action; LBGI, low blood glucose index; MOOD, mean of daily difference; UD, Unstable diabetes; HGV, High glycemic variability; LGV, low glycemic variability; IDeg, Insulin degludec

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insulin [2], which leads to an increased number of visits and hospitalizations [3].

The risk of asymptomatic hypoglycemia is directly related to increased glycemic variability (GV) [4,5], therefore, it has been proposed that reducing fluctuations in glucose levels should be considered as an important issue in the development and evaluation of new therapies; additionally, glycemic variability should be an assessed outcome [6].

Insulin degludec (IDeg) is an ultralong-acting basal insulin that is available for the management of patients with DM1 and DM2. Its effect is based on the formation of soluble multi-hexamers in subcutaneous tissues, creating a depot from which monomers are released slowly and continuously, to be finally absorbed into the blood flow; this leads to a more stable pharmacokinetic profile, and lower fluctuations in glucose levels [7]. These characteristics, particular to IDeg, should bring greater clinical benefits to those patients with increased glycemic variability, however, its effect has not been formally assessed in such population.

The aim of this pilot study is to assess the impact of the switch from a Glargine or Detemir insulin regimen to a basal insulin regimen with IDeg on GV, measured by continuous glucose monitoring (CGM), on metabolic control and on the incidence of hypoglycemia episodes in a group of patients with and without unstable diabetes, defined as increased GV.

Methods

A prospective before-after study was conducted, including patients treated at the diabetes center of Hospital Universitario San Ignacio in Bogotá, Colombia. Recruitment was conducted along the period between May 2015 and September 2016. Patients with DM1 or DM2 older than 18 years were recruited, who were under continuous treatment with a basal insulin, basal bolus or basal plus regimen (including Insulin Glargine or Insulin Detemir) for at least 3 months, and had A1c levels > 7% (53 mmol/mol) or recurrent episodes of non-severe symptomatic hypoglycemia. Exclusion criteria were: medical history of severe recurrent hypoglycemia, liver failure or Child type B or C liver cirrhosis, renal failure at stage 5 (glomerular filtration rate < 15 mg/dL) or active oncological disease. The protocol was approved by the ethics committee of Hospital Universitario San Ignacio and Pontificia Universidad Javeriana.

In a first visit, data on baseline demographic and clinical characteristics were obtained from an interview with the patient and from the systematic records kept in his/her medical history. All baseline A1c measurements were processed using techniques approved by the National Glycohemoglobin Standardization Program (NGSP). Those who met the inclusion criteria were requested to sign an informed consent.

At that same visit, an CGM equipment was set using the iPRO2® device (Medtronic, Northridge, CA). The Enlite sensor (Medtronic, Minneapolis, MN) was inserted subcutaneously into the anterior abdomen area and held in place for 6 days. Calibration of the CGM device was performed following the recommendations of the iPRO2® manufacturer by capillary glucose measurements at the first and third hour after the insertion of the subcutaneous sensor, and then measurements were made before each meal, until the end of the study. At the end of 6 days, the device was removed and data downloaded using the iPRO CareLink version 3.0 software. Subsequently, treatment with Degludec insulin (IDeg) was started. Because all the patients had history of hypoglycemia, the IDeg initial dose was calculated by reducing the previous requirements of Glargine or Detemir insulin by 20% for each patient. The dose was titrated on the basis of fasting blood glucose levels with a target of 91–126 mg/dL (5.1–7.0 mmol/L). Patients were asked to avoid intense physical activity, to maintain a diet similar to that previously received and to inform the investigators about any changes in the device insertion site.

After 12 weeks of IDeg treatment, a second CGM was performed, following the same guidelines as for the initial CGM. At the end of the study, new samples were taken for A1c measurement. Data obtained from CGM were exported for analysis by a calculation software in MATLAB®, where records were pre-processed to discard those days with consecutive losses greater than 50 samples. Lower losses were linearly interpolated. Based on these data, different metrics of glycemic variability and glycemic risk were calculated, including standard deviation (SD), coefficient of variation (CV), mean absolute glucose change (MAG), interquartile range (IQR), mean of daily difference (MODD), continuous overall net glycemic action (CONGA 1, 2 and 4 h), low blood glucose index (LBGI) and mean amplitude of glucose excursion (MAGE).

An episode of clinically significant hypoglycemia was defined as interstitial glucose levels lower than 54 mg/dL for at least 20 min [8,9], and nocturnal hypoglycemia was defined as those episodes which occurred between 00:01 and 05:59 [10,11].

For continuous variables, mean and standard deviations are reported for normal distribution variables, or median, and interquartile range were reported if this assumption was not met. For categorical variables, frequency and percentages tables are reported. Based on the results of the first CGM, patients were classified according with basal CV values on low glycemic variability (LGV) or high glycemic variability (HGV), with a coefficient of variation threshold of 34% [12]. A sensitivity analysis was conducted using a cut point of 36%, as suggested by Monnier to define unstable diabetes (UD), with similar results [13]. To assess the change over time for each subgroup in A1c levels, glycemic variability measurements and in mean insulin doses, a paired *t*-test or a Wilcoxon signed rank test were used, comparing baseline values with values after 12 weeks of the switch of the treatment. The incidence of global and nocturnal hypoglycemia before and after treatment with IDeg was compared using a McNemar chi-square test.

In order to estimate the trend over time on glycemic variability measured with the CV, and A1c levels we additionally performed a longitudinal analysis using generalized estimating equations (GEE). The advantage of GEE is that it take into account the fact that the serial observations of the same patient are autocorrelated, and let us to evaluate how the average of a response variable of a subject changes with covariates. In the present study, an exchangeable correlation structure was used. As a sensitivity analysis, we fitted GEE models also assuming either an unstructured or an “independent” correlation structure, without significant changes in the results. Multivariable GEE was used to identify the coefficients of each covariate for the presented response variables after stratifying the patients as LGV or HGV according with the basal CV measure. The time model with a significant contribution (p-value < 0.05) and the lowest quasi-likelihood information criterion (QIC) represents the best model for the data [14]. A statistical STATA 15.0 package was used for the analyses.

Results

60 patients were invited to participate and underwent the first CGM. Most patients had type 2 diabetes (72.4%); they were mainly women (55%), receiving Insulin Glargine (66.6%), and a basal bolus regimen (71.6%) before switching to IDeg. The mean A1c value pre-treatment was 8.28% (67 mmol/mol) ± 1.74% and after 12 weeks of treatment with IDeg was 7.16% (55 mmol/mol) ± 1.54%. The mean difference was −1.04% (95% CI, −0.42, −1.67), p = 0.0013. The mean TDD was reduced from 0.45 units per kg of weight during the pre-intervention period to 0.37 units per kg of weight after 12 weeks of IDeg treatment (p = 0.022) in all patients recruited.

The demographic and clinical data of patients according with basal glycemic variability sub groups are shown in Table 1. 42 patients were classified as LGV and 18 had basal CV values higher than 34% and were classified as HGV. Patients with HGV had significatively higher values of A1c (8.84% ± 2.08 vs 7.63 ± 1.31. p = 0.01), and used higher dose of basal insulin (0.40 ± 0.21 U/kg vs 0.58 ± 0.51 U/kg. p = 0.01) The indication of degludec was different between groups