A pilot study comparing the CGM-assessed glycemic profiles of patients with type 1 diabetes on insulin degludec and insulin glargine

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Abstract

Aims To compare the diurnal glycemic profiles obtained with basal insulin degludec (InsDeg) and basal insulin glargine (InsGla) in patients with type 1 diabetes using continuous glucose monitoring (CGM) in an outpatient setting.

Methods Twenty Japanese patients with type 1 diabetes who were using once-daily InsGla before supper as part of their multiple daily insulin injections were consecutively recruited. CGM was initiated before supper on day 1, and InsGla was switched to InsDeg at the same dose on day 3. The average CGM glucose profile obtained on days 1 and 2 was compared with the corresponding profile for days 5 and 6. The bolus insulin regimen was not changed during the study period.

Results CGM glucose was significantly higher ($p < 0.05$) from 19:30 to 22:30 and significantly lower ($p < 0.05$) from 6:30 to 8:00 with basal InsDeg than with basal InsGla.

The duration of hypoglycemia (<70 mg/dl) was the same regardless of whether basal InsDeg or basal InsGla was used.

Conclusions The peak in the action profile of InsDeg lasts longer and is possibly stronger than that of InsGla.

Keywords Insulin degludec · Insulin glargine · Type 1 diabetes · Continuous glucose monitoring (CGM)

Introduction

Insulin degludec (InsDeg) is a newly developed, ultra-long-acting insulin that is released slowly from soluble multi-hexamers which form after subcutaneous injection, resulting in a long half-life and stable and smooth pharmacokinetic and pharmacodynamic profiles [1]. Treatment with InsDeg is reported to reduce the incidence of nocturnal hypoglycemia by 25 % compared with insulin glargine (InsGla) in patients with type 1 diabetes [2]. However, there are no reports of the use of continuous glucose monitoring to compare the glucose profiles obtained with InsDeg and InsGla. In the study reported in the present paper, continuous glucose monitoring (CGM) was employed to compare the efficacies of InsDeg and InsGla when taken at the same dose level by patients with type 1 diabetes in an outpatient setting.

Subjects, materials, and methods

Study population

Twenty Japanese patients with type 1 diabetes were recruited consecutively from November 2012 until October

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2013 at Terasawa Hospital and at Tokushima University Hospital. The subjects were treated with multiple daily insulin injections including once-daily InsGla before supper, and their dose of InsGla was titrated to adjust for bedtime and fasting blood glucose equally. Individuals who were pregnant or had unstable retinopathy or an eating disorder, those who were night-shift workers, and those who were using other medications that affect blood glucose (i.e., steroids) were excluded. All subjects provided written informed consent. This study was approved by the institutional ethics committee and was also registered in the clinical research registry (UMIN 000011293).

Self-monitoring of blood glucose was performed at least four times daily (premeal and before sleep) during the study period. The participants were instructed to take meals with 25–30 kcal/kg ideal body weight consisting of 50–60 % carbohydrate, 20–25 % fat, and 15–20 % protein. The bolus insulin regimen (i.e., correction insulin or carbohydrate-to-insulin ratio) was not changed during the study period. Bedtime correction bolus insulin was applied the same way regardless of whether basal InsGla or InsDeg was being taken by the patients. Patients' physical activity was variable, from sedentary to mildly active. Moderate to marked activity was limited.

CGM

CGM was initiated for the patients on day 1. An Enlite sensor (Medtronic, Northridge, CA, USA) was used by these patients for 7 days. Basal InsGla was switched to basal InsDeg at the same dose on day 3. Because it took approximately 3 days for once-daily injection of InsDeg to achieve a steady condition [3], blood glucose profiles determined with CGM on day 1 and day 2 were compared with those obtained on day 5 and day 6 (the 3rd and 4th day of InsDeg). CGM data were regarded as acquired if CGM data were obtained more than 90 % of the time.

Statistical analysis

Age, duration of diabetes, body mass index (BMI), and total daily insulin dose were collected at the beginning of this study. Hypoglycemia was defined as less than 70 mg/dl of CGM glucose, and the duration of hypoglycemia was compared between the two drug periods (i.e., when InsGla was being taken and when InsDeg was being taken). Demographic data are presented as the mean $\pm$ standard deviation. A mixed model with patients as a random variable was used to estimate the mean glucose at each time point during each drug period (basal InsGla or InsDeg), and to compare the mean values obtained during both drug periods at each time point. The difference in hypoglycemia duration between the drug periods was

tested using Fisher's exact test. A *p* value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SAS ver. 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

CGM data were successfully acquired from 16 of the 20 participants. Characteristics of the 16 patients are shown in Table 1. The average CGM glucose values on days 1 and 2 (i.e., basal InsGla) and days 5 and 6 (basal InsDeg) are shown in Fig. 1. Glucose was significantly higher ($p < 0.05$) from 19:30 to 22:30 and significantly lower ($p < 0.05$) at 6:30 to 8:00 when the patients were taking InsDeg (the "InsDeg period") as compared to when they were taking InsGla (the "InsGla period," $p < 0.05$). The average amount of correction bolus insulin before bed was the same regardless of whether InsDeg or InsGla was being taken (1.03 ± 1.31 v.s. 0.88 ± 1.79 units, $p = 0.60$).

The average 24-h glucose values were comparable (InsDeg period, 142.6 ± 5.8 ; InsGla period, 143.1 ± 5.9 mg/dl). The hypoglycemia duration per day and the hypoglycemia duration during the interval from 23:00 to 07:00 did not differ between the InsDeg and InsGla periods (data not shown). The intraday standard error of the glucose value (mg/dl) also did not differ between the InsDeg and InsGla periods (data not shown). However, the intraday standard error of the glucose value during the interval from 23:00 to 07:00 was significantly less during the InsDeg period than during the InsGla period [InsDeg period, 39.3 (38.4–40.3; 95 % confidence interval); InsGla period, 46.2 (45.1–47.4), $p < 0.001$].

Table 1 Characteristics of study patients

Characteristics	<i>n</i> = 16
Age (years)	53.9 $\pm$ 17.3
Gender (male/female)	9/7
Weight (kg)	56.3 $\pm$ 10.9
BMI (kg/m ²)	21.9 $\pm$ 3.1
Diabetes duration (years)	15.4 $\pm$ 12.1
HbA _{1c} (NGSP, %)	7.2 $\pm$ 1.0
Total daily dose of insulin (U/day)	37.7 $\pm$ 20.4
Total daily dose of basal insulin (U/day)	11.6 $\pm$ 6.4
Serum c-peptide (ng/ml)	0.63 $\pm$ 1.58
GAD antibody (U/ml)	91.1 $\pm$ 290.7

Data are expressed as the mean $\pm$ standard deviation

BMI body mass index, GAD glutamic acid decarboxylase autoantibodies

Fig. 1 The average CGM glucose data on days 1 and 2 (i.e., basal InsGla, *closed circles*) and on days 5 and 6 (basal InsDeg, *open circles*). The data are presented as the mean $\pm$ standard error. Glucose levels were significantly higher from 19:30 to 22:30 ($p < 0.05$) and significantly lower from 6:30 to 8:00 ($p < 0.05$) with basal InsDeg than with basal InsGla

Discussion

The efficacies of basal InsGla and InsDeg (at the same dose) based on the glucose profiles of 16 patients with type 1 diabetes were investigated using CGM. InsGla has been reported to reach peak insulin action 4–5 h after injection [4, 5], whereas InsDeg is reported to exhibit a flat time profile of glucose-lowering action [6]. Morning glucose was significantly lower with InsDeg than with InsGla (Fig. 1). Because the correction bolus insulin amount before bed was the same during the InsDeg and the InsGla periods, InsDeg appears to exert a stronger action than InsGla around dawn.

InsDeg was reported to reach peak insulin action approximately 12 h after injection [5]. The basal insulin requirement is usually increased to suppress glucose excursion at dawn (the “dawn phenomenon”) in patients with type 1 diabetes [7]. The peak action profile of InsDeg taken at supper seems to correspond with the dawn phenomenon. Although the 24-h glucose values were comparable during the InsDeg and the InsGla periods, the standard error of the glucose value during the interval from 23:00 to 7:00 was significantly lower with InsDeg than with InsGla. Therefore, it seems that treatment with InsDeg suppresses nocturnal blood glucose fluctuations in patients with type 1 diabetes when compared to treatment with InsGla (Fig. 1). These pharmacodynamics of InsDeg could result in a better indication for patients who suffer from the dawn phenomenon when using InsGla.

Although the bolus insulin regimen used did not change throughout the study, post-supper glucose was significantly higher with InsDeg than with InsGla (Fig. 1), which agrees with previous reports [4–6]. It may be better to increase the bolus insulin dose at suppertime to suppress any post-supper glucose excursion when switching from InsGla to InsDeg, with the same dose used before supper.

There are several reports of trials that compare InsGla and InsDeg in a treat-to-target manner in patients with type 2 diabetes who were naïve to insulin [8] and in patients with type 1 diabetes [2]. In those trials, the dose of InsDeg was 10–20 % lower than that of InsGla at the end of the study [2, 8]. Taken together with the present results, there are two possibilities, i.e., the duration of peak action is longer and the action profile may be stronger for InsDeg than for InsGla at the same insulin dose in patients with type 1 diabetes. In our study, the incidence and duration of hypoglycemia did not differ between the InsGla and InsDeg periods. Our study did not use a treat-to-target approach, which may be why we did not obtain the same results as in [2, 8]. Also, our patients were all Japanese patients with type 1 diabetes, so there may have been a racial difference.

Limitations of this study include its small sample size and the fact that mealtimes and the contents of the meals were not set for each patient. It was reported previously that once-daily injection of InsDeg results in a steady condition within approximately 3 days [3], but there is the possibility that there was not a steady condition on the third day of InsDeg; indeed, in a study by Heise et al. [6], measurements were taken after 6 days of treatment with InsDeg.

In conclusion, the peak in the action profile for InsDeg lasts longer and may be stronger than that of InsGla at the same insulin dose in patients with type 1 diabetes.

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Compliance with ethical standards

Conflict of interest MM received honoraria from Sanofi, which markets insulin glargine.

Human rights and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients before they were included in the study.

References

- Jonassen I, Havelund S, Hoeg-Jensen T, et al. Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. *Pharm Res.* 2012;29:2104–14.
- Heller S, Buse J, Fisher M, BEGIN Basal-Bolus Type 1 Trial Investigators, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet.* 2012;379:1489–97.

3. Zinman B. Newer insulin analogs: advances in basal insulin replacement. *Diabetes Obes Metab.* 2013;15(Suppl 1):6–10.
4. Porcellati F, Rossetti P, Busciantella NR, et al. Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes: a double-blind, randomized, crossover study. *Diabetes Care.* 2007;30:2447–52.
5. Atkin S, Javed Z, Fulcher G. Insulin degludec and insulin aspart: novel insulins for the management of diabetes mellitus. *Ther Adv Chronic Dis.* 2015;6:375–88.
6. Heise T, Nosek L, Bottcher SG, et al. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. *Diabetes Obes Metab.* 2012;14:944–50.
7. Kuroda A, Kaneto H, Yasuda T, et al. Basal insulin requirement is ~30 % of the total daily insulin dose in type 1 diabetic patients who use the insulin pump. *Diabetes Care.* 2011;34:1089–90.
8. Heise T, Tack CJ, Cuddihy R, et al. A new-generation ultra-long-acting basal insulin with a bolus boost compared with insulin glargine in insulin-naïve people with type 2 diabetes: a randomized, controlled trial. *Diabetes Care.* 2011;34:669–74.