Original Article

CONTRIBUTION OF THE DAWN PHENOMENON TO THE FASTING AND POSTBREAKFAST HYPERGLYCEMIA IN TYPE 1 DIABETES TREATED WITH ONCE-NIGHTLY INSULIN GLARGINE

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ABSTRACT

Objective: To observe the effect of the dawn phenomenon on basal glucose and postbreakfast hyperglycemia in patients with type 1 diabetes treated with once-nightly insulin glargine and premeal insulin lispro.

Methods: In 49 study subjects consuming a fixed isocaloric (50% carbohydrate) diet of usual food, the insulin glargine dose was titrated from daily continuous glucose monitoring downloads to achieve a basal glucose goal of <130 mg/dL 4 hours after meals and during serial meal omissions but with fewer than 10% of readings at <70 mg/dL during 24 hours. Patients also performed self-monitoring of plasma glucose 7 times a day (before and 2 hours after each meal or omitted meal and at bedtime).

Results: The target mean basal glucose level was achieved only during the non-dawn phenomenon period (1400 hours to 0400 hours). During the dawn phenomenon, the mean (standard deviation) basal glucose level increased from 118 (57) mg/dL at 0400 hours to 156 (67) mg/dL before the breakfast meal, a 32% increase (P = .00149). The mean self-monitored plasma glucose level with meal omission was 63.8% of that increase with a breakfast meal.

Conclusion: The fasting morning glucose concentration is considerably elevated because of the dawn phenomenon. Targeting insulin titration to this glucose level may result in excessive basal insulin dosing for the non-dawn phenomenon periods of the day. The dawn phenomenon is a large component of the postbreakfast hyperglycemia. Rather than increasing the morning premeal insulin bolus, consideration should be given to pretreating the earlier dawn phenomenon with an insulin pump with use of a variable basal insulin rate. **(Endocr Pract. 2012;18:558-562)**

Abbreviations:
A1C = hemoglobin A_{1c}; **CF** = correction factor; **CGM** = continuous glucose monitoring; **ICR** = insulin-to-carbohydrate ratio; **SMPG** = self-monitoring of plasma glucose

INTRODUCTION

In a previous study (1), in which we evaluated the mathematical dosing relationships in patients with type 1 diabetes who were treated with once-nightly insulin glargine and a premeal bolus of insulin lispro, we observed the contribution of the dawn phenomenon to the fasting morning glucose level (the commonly used titration target for basal insulin) and to the hyperglycemia after the breakfast meal. In this current report, we describe those observations.

RESEARCH DESIGN AND METHODS

This single-center study was approved by the institutional review board and conducted in accordance with the Declaration of Helsinki. For this study, 52 patients with type 1 diabetes treated with multiple daily insulin injections were enrolled and signed informed consent documents.

The inclusion criteria were as follows: ≥18 years of age; diagnosis of type 1 diabetes; duration of diabetes ≥3 months; treatment with multiple daily insulin injections

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for ≥6 weeks; hemoglobin A_{1c} (A1C) level ≤9.0%; <1% A1C change during the previous 3 months; adherence to office appointments and health care provider instructions; and attendance of a class or demonstration of knowledge regarding carbohydrate counting. Type 1 diabetes was defined as the presence of insulin-requiring disease with onset at <40 years of age, a random C-peptide value of <1.0 ng/mL, glutamic acid decarboxylase-65 antibody positivity, or a history of diabetic ketoacidosis.

The following were exclusion criteria: a major surgical procedure, infection, or psychologic stress during or within 6 weeks before the study; treatment with a medication that influences insulin sensitivity (for example, prednisone, a β-blocking agent, or a diuretic); timing within 1 week of menses; unstable eating or activity pattern; pregnancy or nursing; working night shift; weight gain of ≥1.5 kg during the preceding 3 months; serum creatinine level of ≥1.5 mg/dL; active liver disease; evidence of autonomic neuropathy, especially gastroparesis; and use of any antiglycemic medication other than insulin or treatment with an insulin pump.

Besides continuous glucose monitoring (CGM), each study subject was instructed to perform self-monitoring of plasma glucose (SMPG) 7 times per day (before and 2 hours after each meal and at bedtime) (Ultra 2, LifeScan, Johnson & Johnson). Each patient was given a list of foods and amounts so that each meal would be isocaloric and provided 50% carbohydrates, 30% fat, and 20% protein. Meals were restricted to 3 a day, and between-meal snacks were not allowed. Compliance was evaluated at each visit by patient recall and a patient diary that included the type and amount of food actually consumed, the time of meals, and the number and timing of glucose tablets used to treat hypoglycemia. After a review of the insulin injection method, each patient was instructed to inject insulin glargine once between 2000 and 2100 hours each evening. The dose was adjusted to achieve a basal glucose level for the entire 24-hour period of <130 mg/dL but with fewer than 10% of the 24-hour readings at <70 mg/dL. The basal glucose level during a meal period, beginning with the usual mealtime plus the subsequent 4 hours, was ascertained by omitting a meal each day in the sequence of dinner, lunch, and then breakfast. Before each meal, a dose of insulin lispro was given, with the amount based on the premeal SMPG value and the meal carbohydrates to be consumed. Because the patients consumed the same amount at each meal, the investigator established the dose of insulin for the meal carbohydrates. The patients adjusted the dose of insulin lispro for an elevated glucose level according to the correction factor (CF). The investigator adjusted the insulin-to-carbohydrate ratio (ICR) at each visit, if needed, to achieve a CGM concentration of ±20% of the premeal glucose level within 2 to 4 postmeal hours. If the ICR was changed, the CF was also changed according to the following formula (2): CF = 4.5 × ICR. The CF was not independently evaluated. Only glucose tablets, 4 g/tablet, were used to treat hypoglycemia.

On the Friday before each study week, an iPRO (Medtronic, Northridge, California) sensor was inserted in accordance with the manufacturer's recommendations. The following week, the study subject reported daily to the center for review of the CGM tracing and for adjustment of the insulin dosing, if indicated. The duration of each visit was about 30 minutes. The basal day was selected when the patient had attained the basal glucose goal for ≥2 days with a constant dose of insulin glargine, <5% of the CGM readings were missing, and the correlation between the SMPG value and the CGM readings was >0.90. The complete 24-hour basal glucose tracing was obtained by substituting a 4-hour omitted meal period for a meal eaten during the selected basal day.

For all results, the mean, standard deviation or error, and range were determined. Tests of significance were 1-tailed *t* tests with 2 samples of equal variance.

RESULTS

Of the 52 study subjects enrolled, 2 withdrew consent for participation before beginning the titration, and 1 was titrated off basal insulin. The C-peptide value for the last-mentioned patient was 0.6 ng/mL, and the glutamic acid decarboxylase-65 antibody was positive. Of the remaining 49 patients, 40% were female. The mean (standard deviation; range) age was 45 (18; 18 to 77) years; duration of diabetes was 12.9 (10.1; 0.5 to 42) years; A1C value was 7.56% (0.74%; 6.2% to 9.0%); random C-peptide level was 0.81 (1.34; undetectable to 5.8) ng/mL; body mass index was 29.4 (5.6; 20.3 to 47.3) kg/m^2; and weight was 84.7 (17.7; 48.8 to 120.9) kg.

The study required a mean of 6.0 (1.5) daily outpatient visits to achieve the titration goal. A mean of 1.5 (0.7) sensors were used per patient. The missing data during the 24-hour selected tracing consisted of <1%. The correlation coefficients for data comparing SMPG and CGM readings were >0.90. Other than mild hypoglycemia (SMPG values of <70 mg/dL with symptoms of hypoglycemia but not necessitating the assistance of another person), there were no adverse events. There was no significant change in weight during titration ($P = .720$).

The 24-hour basal glucose target was <130 mg/dL but with fewer than 10% of the readings <70 mg/dL. This goal was achieved but only during the non-dawn phenomenon portion of the day (1400 hours to 0400 hours). For this portion, the mean CGM value was 120 (52) mg/dL, with 7.2% of readings <70 mg/dL. During the titration, attempts to achieve a basal glucose level of <130 mg/dL during the dawn phenomenon were associated with hypoglycemia during the other portions of the day, especially if the noon or supper meals were omitted. Thereafter, we targeted basal glucose control only during the non-dawn phenomenon

portion of the day. The dawn phenomenon (Fig. 1) began at 0400 hours at a mean CGM value of 118 (57) mg/dL, increased to 156 (67) mg/dL (a 32% increase; $P = .00149$) at the mean breakfast time of 0730 hours, and peaked at 1000 hours at a mean CGM level of 173 (88) mg/dL (a 47% increase; $P = .000182$) before returning to baseline at 1400 hours at a mean CGM value of 123 (61) mg/dL. The dawn phenomenon (the difference between the 1000 hours and the 0400 hours CGM levels) increase of >30 mg/dL occurred in 57% and >10 mg/dL occurred in 73% of the study subjects. In those patients with a random C-peptide level <0.6 ng/mL (n = 28), a dawn phenomenon of >30 mg/dL was observed in 75%. The correlation coefficient between the amplitude of the dawn phenomenon and the random C-peptide level was –0.370 ($P<.05$) (Fig. 2); and the duration of diabetes was 0.309 ($P<.05$); and the weight was 0.196 ($P>.05$); and the baseline A1C value was 0.118 ($P>.05$). The mean time at which the study subjects measured their morning fasting SMPG value and ate breakfast was 0727 hours (± 63 minutes), or about 3½ hours after the onset of the dawn phenomenon. The mean time at which lunch and supper were eaten was 1244 hours (± 26 minutes) and 1812 hours (± 52 minutes), respectively.

The mean morning fasting SMPG value (Fig. 3) was 145 (66) mg/dL. The 2-hour postbreakfast-time SMPG level with meal omission was 63.8% of that when the meal was eaten.

The mean insulin glargine dose was 0.27 U/kg at the time of entrance into the study and was 0.21 U/kg at the end of titration. No significant difference was found in the results between women and men in this study.

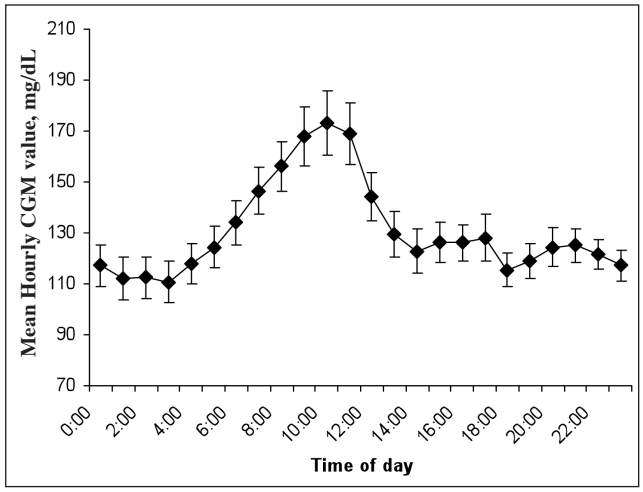

Fig. 1. Hourly mean and standard error basal glucose levels by continuous glucose monitoring (*CGM*) in 49 patients with type 1 diabetes treated with once-nightly insulin glargine. The basal glucose level was determined by once-daily meal omissions and then cutting and pasting the omitted meal periods.

DISCUSSION

The fasting morning glucose level is usually the target of basal insulin titration (3-7). This glucose value may be elevated for reasons other than an insufficient amount of basal insulin. These factors include rebound hyperglycemia from nocturnal hypoglycemia (the Somogyi phenomenon) (8), waning basal insulin action as with NPH insulin (8), a prior late night dinner of high carbohydrates and fats (9), delayed gastric emptying associated with gastroparesis (10), the arousal effect of wakening (11), and the dawn phenomenon (or a combination of these factors). In our study, patients with gastroparesis were excluded, the meals were controlled, and the mean basal glucose level was not low during the early morning hours. The presence of a waning basal insulin effect was unlikely because of the 24-hour duration of the action of insulin glargine (12) and the return to baseline of the basal glucose value in the afternoon. This return could not be attributed to a prior meal insulin bolus because it was given 11 hours earlier whenever the lunch meal and bolus were omitted. We combined the arousal-induced component of the morning hyperglycemia with that of the dawn phenomenon, inasmuch as we could not separate the 2 effects.

The dawn phenomenon was first described in 1924 (13) and more completely in 1985 (14) as a progressive hyperglycemia beginning about 0400 hours and peaking around 1000 hours. The frequency, the magnitude, and even the definition of this phenomenon have varied widely (8,15). In this study, we observed that the phenomenon is frequent—in 75% of study subjects with a minimal C-peptide level and therefore β-cell function—and contributes substantially to the morning hyperglycemia. Focusing on only the fasting glucose level for basal insulin titration could result in an excessive basal insulin dose for the non-dawn phenomenon portion of the basal day. In published trials of once-nightly insulin glargine titration in conjunction with premeal rapid-acting insulin in patients with type 1 diabetes, the mean insulin glargine dose ranged from 0.28 to 0.67 U/kg. In comparison, our mean dose was 0.21 U/kg. It is unclear why more hypoglycemic episodes were not reported in the prior studies. Because eating was not controlled, it could be attributable to defensive eating by the patients to prevent hypoglycemia. Alternatively, hypoglycemia could have been missed as a result of infrequent glucose monitoring or hypoglycemia unawareness from previous repeated episodes. For similar future trials, we suggest that the basal insulin be titrated to other than morning glucose concentrations and that the detection of hypoglycemia be augmented by meal omissions.

We observed that the amplitude of the dawn phenomenon was inversely related to the random C-peptide level. This finding could be explained by the lack of β-cell function to mitigate the increasing morning insulin resistance

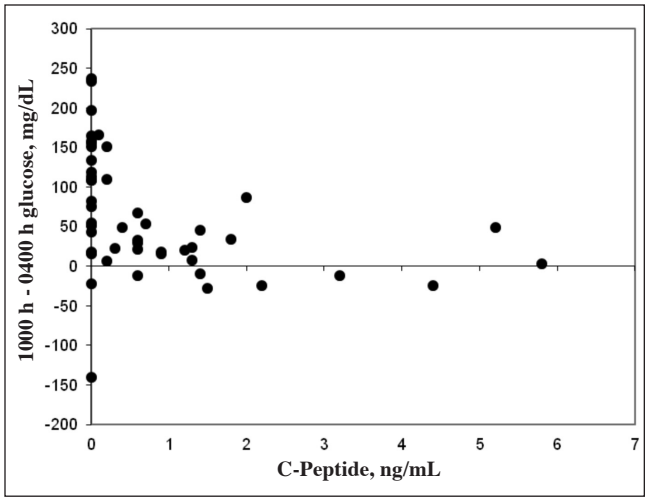

Fig. 2. The relationship between the random C-peptide value and the extent of the dawn phenomenon, as defined as the difference between the 1000 hours and the 0400 hours continuous glucose monitoring values, in 49 patients with type 1 diabetes treated with once-nightly insulin glargine.

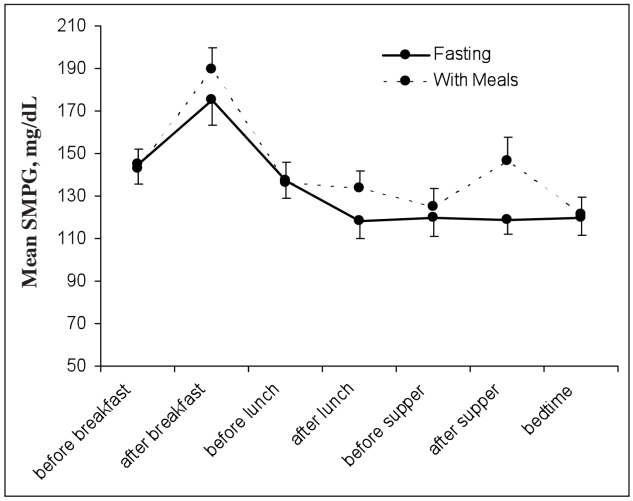

Fig. 3. The mean and standard error self-monitoring of plasma glucose (*SMPG*) values in 49 patients with type 1 diabetes treated with once-nightly insulin glargine and insulin lispro before meals, with meals omitted (fasting) and with meals consumed.

associated with the dawn phenomenon. We excluded those patients with A1C values >9.0% and thus limited our range of study subjects. This factor would diminish our ability to detect an inverse relationship between glucose control and the extent of the dawn phenomenon (16).

It appears that the hyperglycemia associated with the dawn phenomenon overlaps that hyperglycemia related to the breakfast meal. Some investigators have suggested that a larger bolus of insulin is needed with the morning meal, as discussed in a report by Van Cauter et al (8). If the bolus is administered just before breakfast (at 0730 hours in our study), and because the peak action of rapid-acting insulin does not occur until 2 hours later (17) (at 0930 hours in our study), the hyperglycemia associated with the dawn phenomenon would not be treated. Because the dawn phenomenon begins at 0400 hours, one must consider an insulin pump with a variable preprogrammable basal rate with a step-up rate before 0400 hours. We (18) and others (19) have shown that this strategy will suppress the dawn phenomenon and eliminate the need for a larger insulin bolus at breakfast.

Although the current study was conducted in a single center, the patients were representative of a wide range of age, weight, insulin dose, and duration of diabetes, all of which allow a broad application of these results. Even though our technique required our study subjects to report to our clinic daily, this visit was only 30 minutes, and the patients continued with their usual activity (sedentary to mild activity) and ate regular foods.

CONCLUSION

Because of the effect of the dawn phenomenon, targeting titration of once-nightly basal insulin to the morning fasting glucose level may lead to excessive insulin dosing. This situation needs to be considered in future studies of basal insulins. The hyperglycemia associated with the dawn phenomenon overlays the hyperglycemia after the breakfast meal. Correction may necessitate suppression of the dawn phenomenon by use of an insulin pump.

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AUTHOR CONTRIBUTIONS

Dr. Allen B. King developed the research concept, wrote the protocol, reviewed the data, and provided the major effort in writing the manuscript. Dawn Clark reviewed the protocol, provided the major contribution to performing the study, and reviewed and edited the manuscript. Gary S. Wolfe reviewed the protocol, aided in supervision of the research, and reviewed and edited the manuscript.

DISCLOSURE

Dr. Allen B. King has received research grants from, has been a consultant to, and has given lectures on behalf of Amylin Pharmaceuticals, Animas Corporation, LifeScan, Eli Lilly and Company, Medtronic, Novo Nordisk, Roche, sanofi-aventis U.S., and Takeda Pharmaceuticals. The other authors have no multiplicity of interest to disclose.

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