

HOW MUCH DO I GIVE? DOSE ESTIMATION FORMULAS FOR ONCE-NIGHTLY INSULIN GLARGINE AND PREMEAL INSULIN LISPRO IN TYPE 1 DIABETES MELLITUS

Allen B. King, MD, FACE^{1,2}; Dawn Clark, MSN, ANP-BC, CDE¹; Gary S. Wolfe, RN, CCM¹

ABSTRACT

Objective: To evaluate the mathematical relationships between dosing factors in type 1 diabetic patients using multiple daily injections.

Methods: In this single-center, prospective study in type 1 diabetic patients, the basal continuous glucose monitoring glucose target was less than 130 mg/dL with fewer than 10% of 24-hour readings at less than 70 mg/dL. Basal glucose for the 4-hour meal periods was obtained from once-daily serial meal omissions. On an isocaloric, 50% carbohydrate, fixed diet, the insulin to carbohydrate ratio was adjusted to achieve a 2- to 4-hour postbolus glucose value within $\pm 20\%$ of premeal glucose. For determining dosing formulas, the slope of the linear regression line comparing the variables of weight, total daily dose (TDD), total basal dose (TBD), insulin-to-carbohydrate ratio (ICR), and correction factor (CF) was determined.

Results: Forty-nine patients were included. Titrating insulin glargine to the morning glucose led to hypoglycemia during the rest of the day (2 PM to 4 AM). Therefore the basal glucose target was the nondawn phenomenon

portion of the day. The resulting estimation formulas could be rounded to the following:

$$\text{TBD} = 0.2 \times \text{weight (kg)} \quad \left| \quad \text{TBD} = 0.33 \times \text{TDD} \quad \left| \quad \frac{90}{\text{TBD}} = \text{ICR} = \frac{\text{CF}}{4.5}\right.\right.$$

Conclusions: Smaller insulin glargine doses to achieve control are in contrast to those much larger doses reported in clinical trials in multiple daily injection-treated type 1 diabetes in which the morning fasting glucose is the basal insulin target. (*Endocr Pract.* 2012;18:382-386)

Abbreviations:

CF = correction factor in units/mg/dL; **CGM** = continuous glucose monitoring; **ICR** = insulin to carbohydrate ratio in g/unit; **MDI** = multiple daily injections; **SMPG** = self-monitored plasma glucose; **TBD** = total basal dose in units/day; **TDD** = total daily dose in units/day

INTRODUCTION

Dosing estimation formulas provide a rapid and simple method for dosing initiation, evaluation, and adjustment in patients with type 1 diabetes mellitus treated by an insulin pump. Using continuous glucose monitoring (CGM), structured diet, and meal omissions to evaluate basal and bolus dosing, we have previously reported these formulas (1). Our findings suggest that excessive basal insulin and insufficient bolus insulin had been previously recommended (2,3). In addition, a simple mathematical relationship exists between the dosing factors of total daily dose in units/day (TDD), total basal dose in units/day (TBD), insulin to carbohydrate ratio in g/unit (ICR), and correction factor in units/mg/dL (CF) (1). These relationships are as follows:

$$0.2 \times \text{weight, kg} = \text{TBD} = 0.4 \times \text{TDD} \\ \frac{100}{\text{TBD}} = \text{ICR} = \frac{\text{CF}}{4.5}$$

Submitted for publication October 11, 2011

Accepted for publication December 7, 2011

From the ¹Diabetes Care Center, Salinas, California; ²University of California, San Francisco, California.

Address correspondence to Dr. Allen B. King, Diabetes Care Center, 1260 S Main St, Suite 201, Salinas, CA 93901. E-mail: aking@diabetescarecenter.com.

Published as a Rapid Electronic Article in Press at <http://www.endocrinepractice.org> on March 22, 2012. DOI:10.4158/EP11312.OR

To purchase reprints of this article, please visit: www.aace.com/reprints.

Copyright © 2012 AACE.

This material is protected by US copyright law. To purchase commercial reprints of this article, visit www.aace.com/reprints. For permission to reuse material, please access www.copyright.com or contact the Copyright Clearance Center, Inc. (CCC).

Basal bolus therapy may also be given by multiple daily injections (MDI) with premeal, rapid-acting insulin and basal therapy with once-nightly basal analogue insulin, eg, insulin glargine. However, pump treatment dose estimation formulas may not apply to MDI-treated patients because of the difference in pharmacodynamics between pump-delivered rapid-acting analogue delivered in multiple rates throughout the day and only once-nightly insulin glargine (4). Insulin glargine has a relatively flat action and usually lasts 24 hours (5). However, because it is flat, it cannot accommodate the transient increase in morning insulin resistance, which is referred to as the dawn phenomenon (6).

The purpose of this study was to evaluate the mathematical relationships between dosing factors in MDI-treated type 1 diabetic patients using the same methods as in our previous study (1).

METHODS

This single-center study was approved by an institutional review board and conducted according to the Declaration of Helsinki. All patients who enrolled in the study provided written informed consent before treatment.

Inclusion criteria were the following: 18 years or older; diagnosis of type 1 diabetes; duration of diabetes 3 months or longer; treated by MDI for 6 or more weeks; hemoglobin A_{1c} level of 9.0% or less; less than 1% hemoglobin A_{1c} change in fewer than 3 months; adherence to office appointments and provider instructions; and attendance in a class or demonstration of knowledge of carbohydrate counting. Type 1 diabetes was defined as glucose control dependent on MDI and disease onset at 40 years of age or less, random C-peptide concentration less than 1.0 ng/mL, positive glutamic acid decarboxylase (GAD 65) antibodies, or a history of diabetic ketoacidosis.

Exclusion criteria were the following: major surgery, infection, or psychological stress during or within 6 weeks of the study; treatment with a medication that influences insulin sensitivity (eg, prednisone, β -adrenergic blockers, diuretics, etc); within 1 week of menses; unstable eating or activity pattern; pregnancy or nursing; working night shift; weight gain of 1.5 kg or more during the preceding 3 months; serum creatinine concentration of 1.5 mg/dL or greater; active liver disease; evidence of autonomic neuropathy, especially gastroparesis; and use of any antihyperglycemic medication other than insulin or treatment with a pump.

With CGM-guided adjustments, each patient was instructed to perform 7 self-monitored plasma glucose (SMPG) measurements per day (before and 2 hours after each meal and at bedtime) (Ultra 2, LifeScan, Johnson & Johnson, Milpitas, California). Three of the SMPG measurements were used for calibration of the sensor. Each patient was given lists of foods and amounts, so that each meal would be isocaloric and provide 50% carbohydrate,

30% fat, and 20% protein. Adherence was evaluated each visit by patient recall and the patient's diary, which included the type and amount of food actually eaten, the time of meals, and how many and when glucose tablets were taken for hypoglycemia. After reviewing their insulin injection method, patients were instructed to give themselves an injection of insulin glargine once between 8 PM and 9 PM each evening. The insulin glargine dose was adjusted to achieve a basal glucose concentration for the entire 24-hour period of less than 130 mg/dL, but with fewer than 10% of the 24-hour readings at less than 70 mg/dL. The basal glucose during the 4-hour meal periods was ascertained by omitting meals in the sequence of dinner, lunch, and breakfast. Insulin lispro was given 15 minutes before the meal for the carbohydrates to be consumed and the premeal SMPG. The investigator set the dose given for the meal carbohydrates because the patients consumed the same amount at each meal. The patient adjusted the insulin lispro dose for the elevated glucose according to the CF. With each visit, the investigator adjusted the ICR, if needed, to achieve a glucose concentration of $\pm 20\%$ of the premeal glucose within 2 to 4 postmeal hours. With each ICR adjustment, the CF was also changed according to the following formula (1):

$$CF = 4.5 \times ICR$$

The CF was not independently evaluated. Glucose tablets, 4 g/tablet, were taken for symptomatic hypoglycemia plus an SMPG measurement less than 70 mg/dL.

On the Friday before each study week, an iPro sensor (Medtronic, Northridge, California) was inserted as per manufacturer recommendations. The following week, the patient reported daily to the center for review of the CGM tracing and adjustment of insulin dosing if indicated. Each visit was about 30 minutes. A representative basal day was selected after the patient had attained the basal glucose goal for 2 or more days on a constant dose of insulin glargine, less than 5% of the CGM glucose readings were missing, and the correlation between the SMPG and the CGM glucose readings was greater than 0.90. The full 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 determining dosing formulas, the slope of the linear regression line comparing the variables of weight, TDD, TBD, ICR, and CF was determined. All regression lines were forced through $y = 0$ intercept. The mean, standard deviation, and range were calculated for most variables.

RESULTS

A total of 52 participants with MDI-treated type 1 diabetes were enrolled. Of the 52 participants, 2 withdrew

consent before beginning the titration and 1 was titrated off basal insulin. The latter patient's C-peptide concentration was 0.6 ng/mL and GAD 65 antibodies were detected. Of the remaining 49 patients studied, 41% were female. The mean (\pm standard deviation [range]) age was 45 (\pm 18 [18-77]) years; mean duration of diabetes was 12.9 (\pm 10.1 [0.5-42]) years; mean hemoglobin A_{1c} was 7.56% (\pm 0.74% [6.2%-9.0%]); mean random C-peptide was 0.81 (\pm 1.34 [undetectable-5.8]) ng/mL; mean body mass index was 29.4 (\pm 5.6 [20.3-47.3] kg/m²), and mean weight was 84.7 (\pm 17.7 [48.8-120.9] kg). After titration and the glucose goal was reached, the mean TDD value was 55.9 (\pm 24.1 [13-150]) units/day, mean TBD was 17.9 (\pm 9.3 [4-60]) units/day, mean ICR was 7.8 (\pm 3.5 [3.0-22.0]) g of meal carbohydrates/unit, and mean CF was 35.6 (\pm 15.5 [13-99]) mg/dL/unit. Of the 24-hour basal readings, 7.3% of the glucose readings were less than 70 mg/dL. The postmeal glucose target for ICR of within 20% of the premeal CGM glucose was achieved. The ICR did not vary during the day. We observed no significant difference ($P > .05$) in the meal-related mean SMPG excursion comparing breakfast data with lunch and evening meal data. The CF was not independently determined.

The study required a mean number of 6.0 (\pm 1.5) daily outpatient visits to achieve the titration goal. One and one-half (0.7) sensors were used per patient. Missing data during the 24-hour tracing selected were less than 1%. The correlation coefficients for data selected were greater than 0.90. Other than mild hypoglycemia (SMPG of <70 mg/dL with symptoms of hypoglycemia, but not requiring the assistance of another person), there were no adverse events. There was no significant change in weight during titration ($P = .720$).

In an attempt to achieve a basal glucose concentration less than 130 mg/dL during the morning hours of the dawn phenomenon, hypoglycemia greater than 10% occurred during the nondawn portions of the day (2 PM to 4 AM), especially when the lunch and dinner meals were omitted. The dawn phenomenon began at 4 AM at a mean (\pm standard deviation) CGM glucose concentration of 118 (\pm 57) mg/dL; peaked at 10 AM with a mean CGM glucose concentration of 173 (\pm 88) mg/dL; and returned to baseline at 2 PM with a mean CGM glucose concentration of 123 (\pm 61) mg/dL. Except for this dawn phenomenon period, the mean basal CGM glucose concentration (2 PM to 4 AM) was 120 (\pm 52) mg/dL. The mean time at which the patients ate breakfast was 7:36 AM, or about 3.5 hours after the onset of the dawn phenomenon.

The insulin glargine dose upon entering the study was 0.27 units/kg and at the end of titration, it was 0.21 units/kg. The mathematical relationships among weight, TDD, TBD, ICR, and CF are shown in Table 1 with a comparison with previously reported relationships in similarly analyzed pump-treated patients (1). Because of the avoidance of hypoglycemia during the nondawn phenomenon periods of the day and the resulting lower basal insulin dose, the ratio of TBD to TDD was reduced. Because of the lower TBD, the numerator in the relationship between TBD and ICR was lower. Both relationships were highly correlated (Figs. 1 and 2). The relationship of weight to TBD was poorly correlated. Using rounded results, the resulting mathematical relationships between dosing factors from this study were the following:

$$\frac{90}{\text{TBD}} = \text{ICR} = \frac{\text{CF}}{4.5}$$

Table 1
Dosing Estimation Formulas Derived From Continuous Glucose Monitoring Titration in Pump-Treated Patients Compared With Data From 49 Type 1 Diabetic Patients Treated With Once-Nightly Insulin Glargine and Premeal Insulin Lispro, After Titration By Continuous Glucose Monitoring While on an Isocaloric 50% Carbohydrate Diet

Estimation formulas	"Y" pump treated (1)	"Y" MDI treated (this study)	Correlation coefficient (this study)
TBD = Y × wt, kg	0.20	0.22	0.48
TBD = Y × TDD	0.42	0.32	0.88
ICR = $\frac{Y}{\text{TBD}}$	112	89	0.79

Abbreviations: ICR, insulin to carbohydrate ratio in g/unit; MDI, multiple daily injection; TBD, total basal dose in units/day; TDD, total daily dose in units/day; wt, weight.

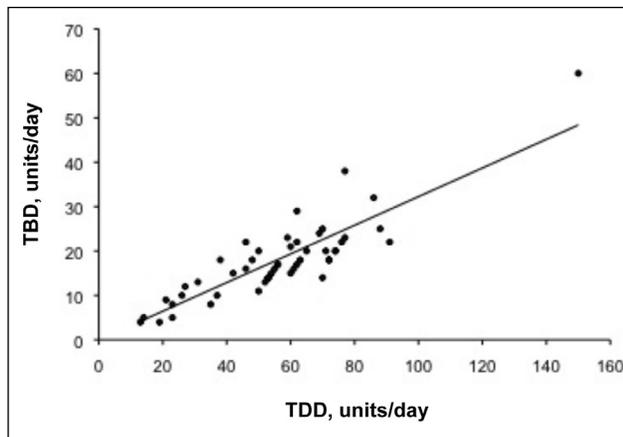


Fig. 1. The total daily dose (TDD) compared with the total basal dose (TBD) in 49 patients with type 1 diabetes mellitus treated with once-nightly insulin glargine and premeal insulin lispro, after titration by continuous glucose monitoring and while following an isocaloric 50% carbohydrate diet.

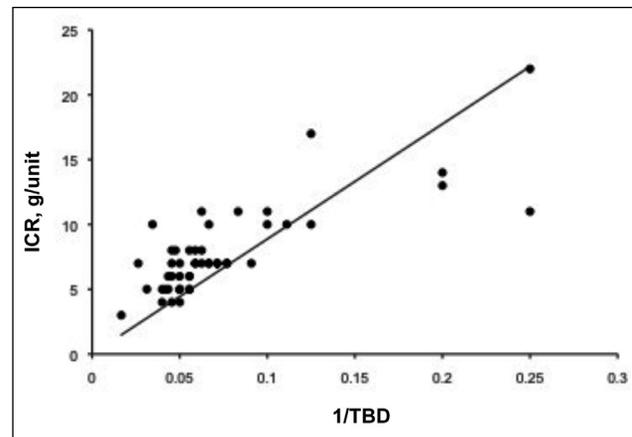


Fig. 2. The reciprocal of total basal dose (TBD) compared with the insulin to carbohydrate ratio (ICR, g of carbohydrates/unit of rapid-acting insulin) in 49 patients with type 1 diabetes mellitus treated with once-nightly insulin glargine and premeal insulin lispro, after titration by continuous glucose monitoring and while following an isocaloric, 50% carbohydrate diet.

DISCUSSION

The glycemic goals for basal glucose control were met during the nondawn portions of the day. In addition, the ICR goal was achieved. CF was not independently studied because we assumed that there would be no difference between a bolus given by injection and a bolus given by an insulin pump.

The results are similar to those in our previous studies (1,7,8); namely, that too much basal and too little bolus insulin are typically used in the clinical setting. Published clinical trials (9-12) of patients similar to those in this study have titrated the basal insulin to higher units/kg. This difference may be in part due to targeting only the fasting morning glucose for titration of once-nightly insulin glargine and not realizing that the morning glucose may be temporarily elevated because of the dawn phenomenon. Although this is a single-center study, the patients studied represent a wide range of characteristics including age, weight, insulin dose, and duration of diabetes, all of which allow broad application of these results. Although our technique did require patients to report to our clinic daily, the visit was only 30 minutes and the patients continued their usual activity (sedentary to mild activity) and ate regular foods.

Because of the reduced basal insulin dose to avoid hypoglycemia during the nondawn phenomenon period, the dosing formulas were different in MDI-treated patients than in pump-treated patients. Confirmation of these formulas will require a prospective trial. In the meantime, these formulas may offer a guide to therapy. We have not studied these formulas in persons with type 2 diabetes, pregnant patients, or pediatric patients. In addition, these

formulas may not apply to those treated with other basal insulin such as neutral protamine Hagedorn or insulin detemir.

CONCLUSION

Smaller insulin glargine doses to achieve glucose control are in contrast to much larger doses reported in clinical trials in multiple daily insulin injection-treated type 1 diabetic patients in which the morning fasting glucose was the basal insulin target.

ACKNOWLEDGMENT

The study was funded by Eli Lilly and Company. This study was presented in abstract form at the 71st American Diabetes Association Scientific Sessions, in San Diego, California, June 24-28, 2011. The authors wish to thank Drs. John Holcombe and David Price for reviewing and commenting on the final manuscript.

DISCLOSURE

Allen B. King has received research grants and has given lectures on behalf of Eli Lilly and Company, sanofi-aventis, and NovoNordisk. Dawn Clark and Gary S. Wolfe have no multiplicity of interest to report.

REFERENCES

1. King AB. How much do I give? Reevaluation of insulin dosing estimation formulas using continuous glucose monitoring. *Endocr Pract.* 2010;16:428-432.

2. **Bode BW.** Insulin pump therapy. In: Lebovitz H, ed. *Therapy for Diabetes Mellitus and Related Disorders, Fourth edition.* Alexandria, VA: American Diabetes Association, 2004: 224-231.
3. **Wolpert H, ed.** *Smart Pumping: For People With Diabetes.* Alexandria, VA: American Diabetes Association, 2002.
4. **King AB, Armstrong D.** A comparison of basal insulin delivery: continuous subcutaneous insulin infusion versus glargine. *Diabetes Care.* 2003;26:1322.
5. **Lepore M, Pampanelli S, Fanelli C, et al.** Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes.* 2000;49:2142-2148.
6. **Campbell PJ, Bolli GB, Cryer PE, Gerich JE.** Pathogenesis of the dawn phenomenon in patients with insulin-dependent diabetes mellitus. Accelerated glucose production and impaired glucose utilization due to nocturnal surges in growth hormone secretion. *N Engl J Med.* 1985;312:1473-1479.
7. **King AB, Armstrong DU.** A prospective evaluation of insulin dosing recommendations in patients with type 1 diabetes at near normal glucose control: bolus dosing. *J Diabetes Sci Technol.* 2007;1:42-46.
8. **King A, Armstrong D.** A prospective evaluation of insulin dosing recommendations in patients with type 1 diabetes at near normal glucose control: basal dosing. *J Diabetes Sci Technol.* 2007;1:36-41.
9. **Birkeland KI, Home PD, Wendisch U, et al.** Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. *Diabetes Care.* 2011;34:661-665.
10. **Bruttomesso D, Crazzolara D, Maran A, et al.** In type 1 diabetic patients with good glycaemic control, blood glucose variability is lower during continuous subcutaneous insulin infusion than during multiple daily injections with insulin glargine. *Diabet Med.* 2008;25:326-332.
11. **Porcellati F, Rossetti P, Pampanelli S, et al.** Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with type 1 diabetes mellitus given meal-time lispro insulin. *Diabet Med.* 2004;21:1213-1220.
12. **Bolli GB, Kerr D, Thomas R, et al.** Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in type 1 diabetes. *Diabetes Care.* 2009;32:1170-1176.