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ORIGINAL ARTICLES

A Prospective Evaluation of Insulin Dosing Recommendations in Patients with Type 1 Diabetes at Near Normal Glucose Control: Bolus Dosing

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Abstract

Background:

Current bolus insulin dosing recommendations are based on retrospective studies of patients with Type 1 diabetes in whom the glucose control was not intensely established. Using continuous glucose monitoring (CGM), we prospectively studied these recommendations in patients treated with continuous subcutaneous insulin infusion.

Methods:

Thirty subjects were studied over a mean of two weeks of continuous glucose monitoring with near daily insulin adjustments. First a basal glucose goal was achieved of <5% of values <70 mg/dl and <20%>, 170mg/dl. Then bolus dosing factors; Insulin to Carbohydrate Ratio (g of meal carbohydrates/unit of insulin, ICR) and Correction Factor (mg/dl fall in blood glucose/unit of insulin, CF); were established for each meal time to a goal of ± 20% of premeal glucose (ICR) or 80-120 mg/dl (CF) by the fourth post bolus hour.

Results:

All treatment goals were achieved in each subject. Modification of formulas from ICR = 450/Total Daily Dose (TDD) to ICR = (217/TDD) + 3 and from CF = 1700/TDD to CF = (1076/TDD) + 12 more closely matched observed results than published formulas. There was no significant difference in each factor with time of day. There was a highly significant relationship between ICR and CF, ICR*4.44 = CF ($r = 0.9$, $p < 0.0005$), total basal dose (TBD) and TDD.

Conclusions:

Current formulas need to be modified to provide higher insulin bolus doses. The interrelationships between ICR, CF, TBD and TDD suggest that any change in one may require a change in the others.

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Abbreviations: (CF) Correction Factor, (CGM) continuous glucose monitoring, (CSII) continuous subcutaneous insulin infusion, (ICR) Insulin to Carbohydrate Ratio, (RAI) Rapid Acting Insulin, (SD) standard deviation, (TBD) total basal dose, (TDD) total daily dose

Keywords: bolus, diabetes, glucose, insulin, pump

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Introduction

Patients treated with basal bolus insulin, using either multiple daily injections or continuous subcutaneous insulin infusion (CSII), must consider both the carbohydrate content of a meal and the prevailing glucose prior to a meal. The carbohydrate content is divided by a factor reflecting the insulin sensitivity. This factor is known as the insulin to carbohydrate ratio (ICR). The current recommended formulas to estimate this factor are 450 divided by the total daily dose (TDD)[1] or 2.8 times the weight (in pounds) divided by the TDD.[1,2] If a patient is to consume 60 grams of carbohydrate and their ICR is 10 g/unit, then 6 units of insulin is injected (100/10 = 10 units). In addition, if the pre-meal glucose is elevated, more insulin is needed. The amount the current glucose exceeds the target glucose is divided by another factor representing insulin sensitivity. This factor is known as the correction factor (CF). The current recommended formula for estimating this factor is 1700 divided by the TDD.[1,2] If the blood glucose is 100 mg/dl higher than target and the CF is 50 mg/dl/unit of insulin, then 2 units of extra insulin is given (100/50 = 2 units).

The formulas for calculating these factors were derived from retrospective observations of 141 Type 1 patients who were treated with CSII for more than 6 months and had an A1C of less than 7.0%.[2] Studies with continuous glucose monitoring (CGM) have demonstrated that A1C does not reflect the daily variation in glucose, especially during the post-meal period.[3,4,5,6]

The purpose of this study was to establish prospectively the bolus factors for patients with Type 1 diabetes treated with CSII using a method of CGM and daily insulin adjustments.[7] We then compared the previously recommended bolus dosing formula results to the observed values. In particular, we studied the mathematical interrelation between dosing formulas to allow estimation of dosing from knowing the value for another dosing factor.

Methods

Subject selection

After obtaining institutional review board approval (Western IRB), subjects were recruited from our patient population from February to May, 2005. Of 324 patients in our Center treated with CSII, 30 patients were consecutively selected who met the inclusion and exclusion criteria and signed an informed consent.

Subjects were included if they were 18 years or older, had been diagnosed with Type 1 diabetes for at least one year, treated with CSII for at least three months, A1C was <8.0% and without detectable fasting C-peptide. Subjects were excluded if their A1C had changed >0.9% within the last six months, were not able to understand and perform carbohydrate counting, had a major stress, e.g., major surgery, serious infection or significant psychological disorder, within last three months or on a medication that would significantly influence insulin sensitivity, e.g., thiazolidinedione, hydrochlorothiazide >12.5 mg/d, and a beta blocker. In addition, subjects were excluded if they were pregnant or nursing, within one week of menses, had a major change in eating or activity patterns, weight change of >1.9 kg within the last three months, a creatinine >1.4 mg/dl, a ALT > three times upper limits of normal or symptomatic gastroparesis.

Protocol

The glucose sensor (CGMS® System Gold, Medtronic, Northridge, California) was inserted on the first day and the monitor activated. On each day(s) thereafter, the patient returned to the Center, where the monitor information was uploaded, without detaching from the sensor, for interpretation and insulin dosage adjustments. The usual duration for each visit was 30 minutes. Each day the monitor was calibrated with four spaced self-monitored blood glucose determinations. The sensor was removed for signal failure, the end of study, or prior to a three day weekend if the sensor had been in place for more than two days before the weekend.

Food was selected by the patient from a separate menu for breakfast, lunch, and dinner and provided an isocaloric diet with a composition of 50% carbohydrate, 30% fat and 20% protein. In all meals the portion sizes were weighed on an electronic scale by the subject. Subjects were told not to change their daily activity except as dictated by wearing the CGM device.

One meal each day was omitted to evaluate the glucose level during that basal period. The glucose target was <5% of all readings < 70 mg/dl and <20%, > 170 mg/dl. The order of once a day meal omission was dinner, lunch, and then breakfast. The results of the basal insulin study are reported in this *Journal*.

Analysis:

After a known amount of carbohydrate was eaten, the ICR was determined from the amount of rapid acting insulin (RAI) needed to return the glucose to ±20% of premeal glucose within four hours. To determine the CF, the premeal insulin bolus was reduced by 25% to produce hyperglycemia by four hours later. Then the CF was determined by the number of units of RAI to return the glucose to 80 – 120 mg/dl within four hours of the bolus. The ICR and CF for each meal time were determined. Subjects were instructed to take glucose tablets, (4 g/tablet) for perceived and confirmed by self-monitored glucose hypoglycemia episodes (<70 mg/dl). A single standard bolus wave was used by all subjects for the ICR and CF studies. All subjects used insulin aspart.

Analysis:

The mean, standard deviation (SD) and range were determined for certain variables. When determining levels of significance for variables in which subjects were compared to themselves, a paired, single-tail test was used. A regression of least squares was used to determine the relationship of variables to each other. The linear equation was set for a y intercept of zero for comparisons of ICR to CF but not with those of ICR or CF to 1/TDD and 1/TBD. The level of significance of such relationships was determined by the correlation coefficient and the degrees of freedom as being N – 1. In addition, formulas for calculating ICR and CF were tested for whether they were significantly different from observed values by an unpaired, two-tailed t test.

Results:

Sixty-seven percent of subjects were female. The subjects' mean (range) age was 46.1 years (20-72); weight, 74.1 kg (48.2-110.1); BMI, 26.1 kg/m^2 (19.5-42.3); duration of diabetes, 19.1 years (2-48); duration of CSII treatment, 5.1 years (1-23); and A1C, 6.98% (6.0-7.9). Of the 30 subjects five were Hispanic American, one was Asian American and the remainder were non-Hispanic Caucasian. The mean (range) TDD was 35.4 units/d (14.7-70); TBD, 13.5 units/d (5.3-30.9); ICR, 10.3 g/unit (5-22.3); and CF, 46.3 mg/dl/unit (21-100).

The sensors functioned for up to eight days and a mean of 2.2 sensors per subject were used. Only two sensors (3%) failed of 65 studies performed. The mean (range) duration of dosage adjustment and glucose assessment was 11.9 days (5-25) and included 8.3 (4-17) Center visits. In all subjects the glucose goals were achieved. For the TBD, the mean percentage of glucose readings below 70 mg/dl were 0.43 % and above >170 mg/dl were 1.56%. The mean (± SD) basal glucose level during the 24-hour period was 115 ± 14 mg/dl. The mean difference between the post-bolus and pre-bolus glucose for all meals was 9.3 ± 3.3 % for ICR. For CF the resulting glucose was ± 10.6 ± 3.7 mg/dl of the 100 mg/dl glucose goal.

The formula for a linear relationship between the ICR and CF to 1/TDD was ICR = (217/TDD) + 3 (**Figure 1**) and CF = (1076/TDD) + 12 (**Figure 2**), respectively. The reported formulas for estimating the ICR of ICR = 450/TDD and ICR = 2.8*Body Weight (lbs)/TDD yielded values that were significantly different from those observed in the subjects ($p < 0.0005$). The formula for estimating CF, CF = 1700/TDD, did not yield results that significantly differed from observed ($p = 0.0873$) but CF = (1076/TDD) + 12 described a more closely associated relationship ($p = 0.833$).

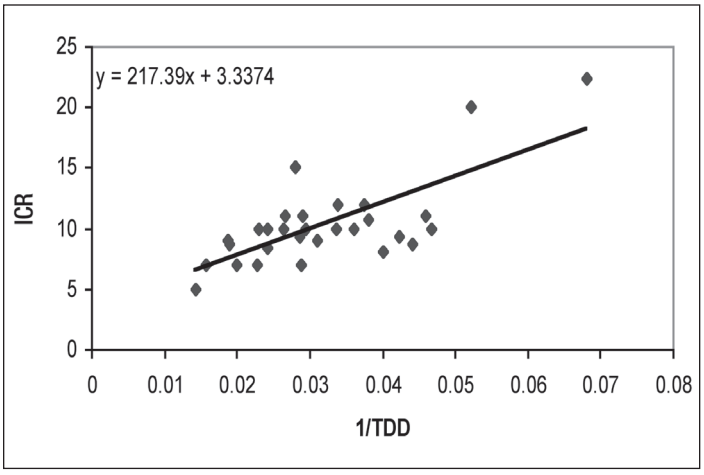

Figure 1. The relationship of the reciprocal of total daily insulin dose (TDD) in units/day to insulin to carbohydrate ratio (ICR) in grams/ unit in 30 ambulatory subjects with Type 1 diabetes treated by continuous subcutaneous insulin infusion at near normal glycemia.

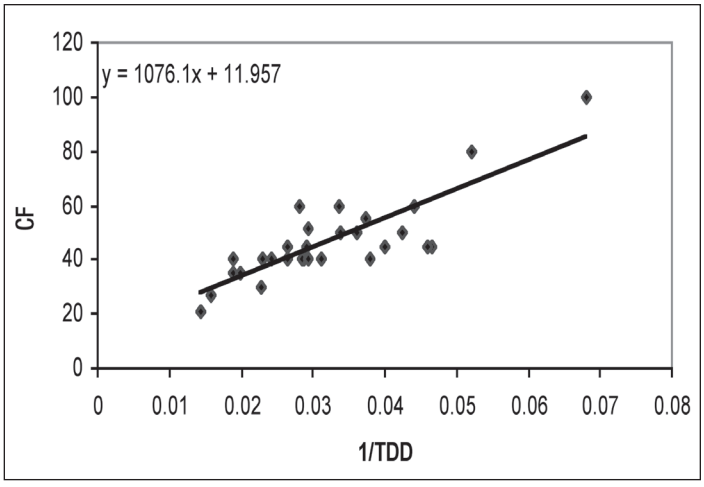

Figure 2. The relationship between the reciprocal of the total daily insulin dose (units/day) to the correction factor (CF) in mg/dl/unit in 30 ambulatory subjects with diabetes treated by continuous subcutaneous insulin infusion at near normal glycemia.

We did not notice any significant difference ($p > 0.05$) in the ICR or CF for different meal times. The mean (standard deviation) ICR for breakfast, lunch and dinner was 10.33 (±3.5), 10.32 (±3.5) and 10.18 (±3.5) g/unit. The CF for these same times was 46.3 (±15.1), 46.5 (±15.1) and 46.3 (±15.4) mg/dl/unit, respectively.

Of note (**Figure 3**) was the highly significant relationship of ICR to CF. When the *y* intercept was forced through zero, the relationship could be represented as 4.44*ICR= CF ($r = 0.900$, $p < 0.0005$). ICR and CF were also significantly related to the reciprocal of the TBD ($r = 0.614$ and 0.662, respectively, and both, $p < 0.0005$) and the TDD ($r = 0.724$ and 0.833, respectively, and both, $p < 0.0005$).

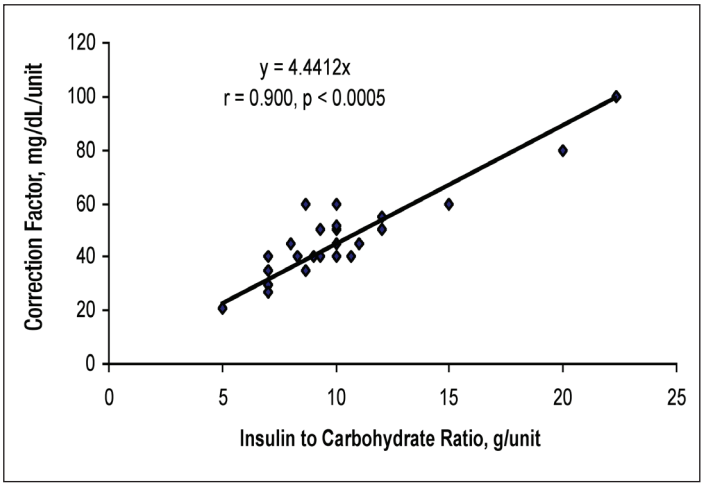

Figure 3. The relationship of insulin to carbohydrate ratio to correction factor in 30 ambulatory subjects with Type 1 diabetes treated by continuous subcutaneous insulin infusion to near normal glycemia.

Discussion

We believe our results can be generalized to a broad population of adult patients with Type 1 diabetes treated by CSII. Our study includes a wide range of ages, diabetes duration, BMI, and several ethnic groups.

The near normal glucose control achieved in this study is a reflection of patient adherence and the combination of daily uploading CGM data, interpretation, and our protocol for insulin dosage adjustments. We achieved a mean (standard deviation) basal glucose level of 115 (±14) and returned the postmeal glucose to about ±10% of the premeal level, both of which allowed for near ideal evaluation for insulin dosing factors and formulas. When established, the basal rate and bolus dosing factors remained stable during the remainder of the study. A longer term attempt at near normal glucose control may be possible since others[8] have demonstrated that insulin sensitivity may remain stable for long periods. Of course this would depend on the patient appropriately counting and bolusing for hyperglycemia and meal carbohydrates.

Our dosing formulas derived from our results differ from those previously reported. Davidson *et al.*[2] used retrospective data from *well controlled*, (defined as an A1C < 7.0%), patients treated with CSII to defined the formulas for ICR and CF. CGM studies[3,4, 5, 6] have revealed that A1C and even occasional self monitored blood glucose data do not adequately reflect postmeal glucose control, which is key in determining proper insulin dosing formulas. Our prospective study was of nearly two weeks duration in ambulatory outpatients in whom activity or sleep were not markedly restricted and had near normal 24 hour glucose control.

The currently recommended formulas for calculating ICR are ICR = 450/TDD (1) and ICR = 2.8* Wt (lbs)/TDD[1,2] and for CF, the formula is CF = 1700/TDD.[1,2] From our data at near normal glucose control we proposed the new formulas of ICR = (217/TDD) + 3 and CF = (1076/TDD) + 12. We did not force the slope of the relationships of ICR and CF to 1/TBD and 1/TDD through $y = 0$ since despite even larger TBD and TDD, the reciprocal would never be zero.

We did not observe a significant difference in ICR or CF between meal times. Some[1] but not all[9] have reported a higher bolus insulin requirement in the morning versus the rest of the day. We believe this may be due to inadequate basal glucose control immediately before, and during these early hours.

The strong relationship between 1/TBD, 1/TDD, ICR and CF (especially the latter two) is not surprising since they reflect the insulin sensitivity of the same organs, liver, muscle, and adipose tissue. Our results suggest that if the one of the factors is adjusted then consideration should be given to change the other.

Our study is limited to those C-peptide negative patients who were well controlled. Because of exclusion criteria we did not study children, pregnancy, stress states, concurrent treatments with medications influencing insulin sensitivity and those patients treated with multiple daily injections using glargine as the basal insulin.

In conclusion, our data support changing dosing formulas. The ICR and CF should be set lower (to yield a higher bolus dose). The 1/TDD, 1/TBD, ICR and the CF are interrelated and any change in one should prompt consideration for change in the others. Lastly, near normal glucose control can be achieved, albeit for two weeks, in selected patients treated with CSII and with insulin adjustments by daily

CGM guided insulin dosage adjustments. Insulin dosing requires clinical judgment and appropriate self-monitoring of blood glucose, since the formula results may vary widely from that observed.

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Disclosures:

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