ANALYSIS OF GUIDELINES FOR BASAL-BOLUS INSULIN DOSING: BASAL INSULIN, CORRECTION FACTOR, AND CARBOHYDRATE-TO-INSULIN RATIO

Paul C. Davidson, MD, FACE, Harry R. Hubblewhite, MS, Robert D. Steed, MD, FACE, and Bruce W. Bode, MD, FACE

ABSTRACT

Objective: To analyze and compare the underlying mathematical models for basal-bolus insulin-dosing guidelines in patients with type 1 diabetes in a retrospective controlled study.

Methods: Algebraic model-development yielded several systems of models with unknown constants, including 3 systems currently in use. These systems were compared for logic and consistency. One of these systems was the accurate insulin management (AIM) system, which we developed in the setting of our large endocrine practice. Our database consisted of retrospective clinical records for a 7-month period. During this time, correction factor (CF), carbohydrate-to-insulin ratio (CIR), and basal insulin were being adjusted incrementally by titration. The variables studied were height, body weight in pounds (BWlb), CF, CIR, hemoglobin A1c (A1C), basal insulin, and 6-day mean total daily dose of insulin (TDD). The values of the variables used in the study were those determined on arrival of the patients at the office. The last 6 TDDs were entered into the database, and the mean was calculated by formulas within the database. We sorted our database into 2 groups, a well-controlled test group (n = 167; A1C ≤7%, time on pump >180 days, no severe hypoglycemic events since the last office visit, and C-peptide level ≤0.5 ng/mL) and a control group with poor control (n = 209; A1C >7% or time on pump <180 days). We obtained one office visit per patient, as follows: from the test group, we chose the visit with the lowest A1C value; from the control group, we chose one visit by use of a computer’s random number generator. A significant difference was demonstrated between the correlation constants of the test group versus the control group by performing T tests between the means and F tests between the standard deviations. The least squares estimates of the correlation constants from the test group were recommended in the guidelines, in place of the means, to gain accuracy. By these methods, the guidelines used by the patients with good glycemic control are made available for all patients.

Results: With use of the AIM system, the TDD for continuous subcutaneous insulin infusion = 0.24 * BWlb; basal insulin = 0.47 * TDD; CF = 1,700/TDD; and CIR = 2.8 * BWlb/TDD.

Conclusion: Three mathematical models for CIR are presented, with a rationale for supporting one of them (the AIM model). This model, together with 3 related AIM models, when provided with statistically correlated constants, constitutes the AIM system of guidelines, a consistent and convenient means of estimating insulin-dosing variables for patients with type 1 diabetes. (Endocr Pract. 2008;14:1095-1101)

INTRODUCTION

Basal-bolus insulin dosing is the widely used method of care for persons with diabetes. It pertains to both insulin pump therapy (continuous subcutaneous insulin infusion) and multiple-dose insulin injection therapy. To calculate insulin boluses, patients are generally taught to use the following 2 simple equations (Eq):

Eq 1. Meal insulin bolus = carbohydrates/carbohydrate-to-insulin ratio (CIR)
Eq 2. Corrective insulin bolus = (blood glucose value – target glucose)/correction factor (CF)

Guidelines are useful for estimating CIR and CF. In addition, a guideline is needed to estimate basal insulin as a fraction of the total daily dose of insulin (TDD). For
patients newly starting insulin pump therapy, whose TDD is not available, a guideline is needed to estimate the TDD on the basis of body weight.

PURPOSE OF THIS STUDY

Our objectives were to examine and compare 3 currently well-known systems of guidelines for insulin dosing and to analyze the mathematical models underlying these guidelines (models are guidelines in which the constants are still unknown). Moreover, we intended to demonstrate that problems are caused by concurrent use of 2 or more guidelines from different systems.

BACKGROUND

The Accurate Insulin Management System

In 1982, Davidson proposed the 1,500 rule for the CF, based on informal clinical observations. In 1998, Steed developed the rule-of-3 for CIR: \( \text{CIR} = 3 \times \text{BWlb/TDD} \), in which \( \text{BWlb} \) is body weight in pounds. In 2002 and 2003, these rules were statistically correlated and presented, together with correlations for basal insulin as a fraction of TDD and for TDD as a function of BWlb, in posters at the American Diabetes Association annual meeting (1,2), Diabetes Technology meeting (3), and International Diabetes Federation Congress (4).

The accurate insulin management (AIM) system bases its guidelines on BWlb and on TDD, whenever it is available. When TDD is not available, it is estimated by an additional AIM formula based on BWlb.

Systems Based on Body Weight Only

The insulin-dosing systems based on body weight make use of the fact that TDD is proportional to body weight to form systems dependent only on body weight (BWlb) at all times. There is no dependence on TDD.

The 400/500 Rule System

The 400/500 rule system varies among its supporters (5-7), but it generally uses a rule of the form \( \text{CIR} = (\text{a constant})/\text{TDD} \), in which the constant ranges from 350 to 600. The other guidelines in this system are generally similar to the AIM system.

RESEARCH DESIGN AND METHODS

Analysis of Models in Different Systems of Guidelines

The analysis of CF and CIR for each system of guidelines begins the same way. The analysis of CF starts with transposing the patient’s formula (equation 2) for CF and placing it in differential form:

**Eq 3.** \( \text{CF} = \frac{\text{[change in (glucose in the blood per unit volume)]}}{\text{[(amount of insulin added)]}} \)

A full day is chosen as the time interval for measurement. The numerator is the amount of glucose metabolized by insulin during the day. The denominator is the volume of glucose-bearing fluid in the body times the TDD:

**Eq 4.** \( \text{CF} = \frac{\text{[glucose metabolized by insulin per day]}}{\text{[glucose volume * TDD]}} \)

The analysis of CIR begins the same way, by transposing the patient’s formula (equation 1) and placing it in differential form:

**Eq 5.** \( \text{CIR} = \frac{\text{[amount of carbohydrates consumed]}}{\text{[amount of insulin added]}} \)

Once again, a full day is chosen as a suitable time interval for measuring the quantities involved. The ratio then becomes as follows:

**Eq 6.** \( \text{CIR} = \frac{\text{[carbohydrates consumed in a day]}}{\text{[meal-related insulin for a day]}} \)

In equations 4 and 6, TDD is easy to measure, but all the other quantities on the right-hand side of the equations are difficult to measure and must be simplified by the use of easy-to-measure surrogate quantities. After this point, the models for the 3 systems of guidelines branch in several different directions, with use of various simplifications. Unknown constants begin with K and are later determined statistically.

The AIM System

**Basal Insulin**

Basal insulin is generally proportional to TDD:

**Eq 7.** \( \text{Basal insulin} = K_1 \times \text{TDD} \)

The constant, \( K_1 \), is determined statistically in a later section.

**Correction Factor**

The starting point is equation 4. The amount of glucose metabolized by insulin per day is generally proportional to body weight; thus, the numerator can be replaced by a constant times body weight: \( K_2 \times \text{BWlb} \). In addition, because glucose volume is proportional to body size, it too can be replaced by a constant times body weight: \( K_3 \times \text{BWlb} \). Accordingly, the following equation arises:

**Eq 8.** \( \text{CF} = \frac{(K_2 \times \text{BWlb})}{(\text{TDD} \times K_3 \times \text{BWlb})} \)
The body weights cancel, and the constants combine into a single constant, yielding the following:

**Eq 9.** \( CF = K4/TDD \)

The constant, \( K4 \), is determined statistically in a later section.

**Carbohydrate-to-Insulin Ratio**

The starting point is equation 6. The amount of carbohydrate consumed per day is generally proportional to body weight; therefore, the numerator is replaced by a constant times body weight: \( K5 \ast BWlb \). This numerator is very similar to the numerator of equation 5. Meal-related insulin is generally a constant times the TDD—\( K6 \ast TDD \)—leading to the following:

**Eq 10.** \( CIR = (K5 \ast BWlb)/(K6 \ast TDD) \)

The constants combine into one constant, with the following result:

**Eq 11.** \( CIR = K7 \ast BWlb/TDD \)

The constant, \( K7 \), is determined statistically in a later section.

**Total Daily Dose of Insulin**

Total daily dose of insulin is generally proportional to body weight:

**Eq 12.** \( TDD = K8 \ast BWlb \)

This should be consistent for patients with type 1 diabetes but not for those with type 2 diabetes because of insulin resistance. Therefore, patients with type 2 diabetes should be screened from the data. The constant, \( K8 \), is determined statistically in a later section.

**The 400/500 Rule and Its Associated System**

This system is distinguished by its model for CIR, which is analyzed first in the subsequent material.

**Carbohydrate-to-Insulin Ratio**

The starting point is equation 6. The next step is to assume that all people eat the same amount of carbohydrate per day—that is, the carbohydrate consumed per day is a constant, \( K9 \). This differs from the AIM system. Meal-related insulin is replaced (in the same manner as for AIM) by \( K6 \ast TDD \).

**Eq 13.** \( CIR = K9/(K6 \ast TDD) \)

The constants combine into one constant (\( K10 \)), as shown in the resulting equation:

**Eq 14.** \( CIR = K10/TDD \)

The supporters of this system (5-7) cite estimates for \( K10 \) ranging from 350 to 550. The constant is reetermined in a later section from our data because statistical comparisons of regression results are not valid unless conducted with the same data.

**Correction Factor**

The starting point is equation 4. Next, it is assumed that the glucose metabolized per day is constant, \( K11 \), and therefore the same for everyone. Once again, glucose volume in the denominator is assumed to be the constant \( K3 \) times body weight.

**Eq 15.** \( CF = K11/(TDD \ast K3 \ast BWlb) \)

The constants combine and lead to the following:

**Eq 16.** \( CF = K12/(TDD \ast BWlb) \)

Equations 14 and 16 seem to form a system, but in practice, the supporters of the 400/500 rule do not use equation 16. Instead, they use equation 9, based on the AIM model for CF—for example, a 1,500, 1,700, 1,800, or similar rule.

**The Weight-Based System**

The weight-based system was derived by other authors, but for easy understanding, the same models can be obtained from the AIM system by substituting equation 7, the AIM system’s model for TDD based on body weight, into the other AIM models as follows.

**Correction Factor**

**Eq 17.** \( CF = (K2 \ast BWlb)/(K3 \ast BWlb \ast K8 \ast BWlb) \)

Two of the BWlb components cancel, and the constants combine. The result is the following:

**Eq 18.** \( CF = K13/BWlb \)

**Carbohydrate-to-Insulin Ratio**

**Eq 19.** \( CIR = (K5 \ast BWlb)/(K6 \ast K8 \ast BWlb) \)

All instances of BWlb cancel, and the constants combine.

**Eq 20.** \( CIR = K14 \)

Equations 18 and 20 seem to form a system, but in practice, the supporters of the weight-based system do not use equation 20. They use an equation that can be obtained
by substituting AIM equation 12 for TDD into the 400/500 rule model, equation 14, with the following results:

Eq 21. \( \text{CIR} = \frac{K_{15}}{\text{TDD}} \)

Statistical Determination of Unknown Constants for the AIM System and the 400/500 Rule System

A digital medical record database of a large clinical practice collected the data in the form of variables in current use by the patients at the beginning of each visit. These data were sorted into a test group and a control group. The data from the test group were used to determine dosing guidelines to recommend for all patients.

Data Sources

The following data were logged into the database routinely: mean, standard deviation, and frequency of blood glucose values from the blood glucose meter memory; BWlb and hemoglobin A1c (A1C) from direct measurement; CF and CIR from the insulin pump’s program or the previous digital medical records; and basal insulin and the last 7 days’ values of TDD from the pump’s memory. The 7 TDDs were averaged by a formula in the database to yield the figure used in the calculations.

Sampling Criteria

All patients were receiving continuous subcutaneous insulin infusion. All patients had C-peptide levels \( \leq 0.5 \) ng/mL; this screening was to identify patients with type 1 or type 2 diabetes with negligible endogenous insulin.

Test Group

Patients in the test group had good glycemic control, as evidenced by A1C values \( \leq 7\% \), more than 6 months of pump experience, and no recorded severe hypoglycemia. The visit with the lowest A1C value was chosen to provide one clinical visit per patient. The resulting group had 1 patient with type 2 diabetes who had insignificant endogenous insulin. The percentage of patients receiving insulin lispro was 98%; 2% were receiving insulin aspart.

Control Group

One clinical visit per patient was chosen at random by computer from all patients not in the test group.

Statistical Methods

The AIM models were used for the statistical correlations:

- Basal insulin = \( K_1 \times \text{TDD} \)
- CF = \( \frac{K_4}{\text{TDD}} \)
- CIR = \( K_7 \times \frac{\text{BWlb}}{\text{TDD}} \)
- TDD = \( K_8 \times \text{BWlb} \)

Tests of independence were conducted between the test group and the control group, as follows. Lists were made of the correlation constants for every patient in each group: (\( K_1 \) of each patient) = basal insulin/TDD; (\( K_4 \) of each patient) = CF * TDD; (\( K_7 \) of each patient) = CIR * TDD/BWlb; and (\( K_8 \) of each patient) = TDD * BWlb. For each of these lists of \( K \) constants, \( T \) tests and \( F \) tests were conducted between the test group mean versus the control group mean, in order to demonstrate the independence of the 2 groups. The test group’s \( K \) constants (the \( K \) constants) were the intervention being tested, and the A1C values were the outcome measure.

Because some of the data were not normally distributed, the \( K \) constants of the test group were further refined by weighted least squares methods. The axes were chosen in a way that configured each model as a straight line through the origin. The fitted value of each \( K \) constant was the slope of the fitted line through the origin. The resulting values differed slightly from the means.

RESULTS

The results are presented below. The scatterplots with least squares regression lines are shown in Figure 1. The least squares values of the \( K \) constants were rounded to obtain the guidelines.

The AIM System

**Basal Insulin**

- \( \text{Test Group}: n = 167; K_1: \text{mean} = 0.47; \sigma = 0.11; \text{median} = 0.48; \text{least squares value} = 0.47 \)
- \( \text{Control Group}: n = 209; K_1: \text{mean} = 0.48; \sigma = 0.12 \)
- \( T \text{ test}, P < .7; F \text{ test}, P < .05 \)

Eq 22. Guideline: \( \text{Basal insulin} = 0.47 \times \text{TDD} \), in which \( K_1 \) is rounded from the least squares value

**Correction Factor**

- \( \text{Test Group}: n = 167; K_4: \text{mean} = 1,776; \sigma = 443; \text{least squares value} = 1,694 \)
- \( \text{Control Group}: n = 209; K_4: \text{mean} = 1,912; \sigma = 552 \)
- \( T \text{ test}, P < .01; F \text{ test}, P < .003 \)

Eq 23. Guideline: \( \text{CF} = \frac{1,700}{\text{TDD}} \), in which \( K_4 \) is rounded from the least squares value

**Carbohydrate-to-Insulin Ratio**

- \( \text{Test Group}: n = 153; K_7: \text{mean} = 2.86; \sigma = 0.88; \text{median} = 2.82; \text{least squares value} = 2.82 \)
- \( \text{Control Group}: n = 173; K_7: \text{mean} = 3.3; \sigma = 1.48 \)
- \( T \text{ test}, P < .004; F \text{ test}, P < .0001 \)

Eq 24. Guideline: \( \text{CIR} = 2.8 \times \frac{\text{BWlb}}{\text{TDD}} \), in which \( K_7 \) is rounded from the least squares value

**Total Daily Dose of Insulin**

- \( \text{Test Group}: n = 166; K_8: \text{mean} = 0.25; \sigma = 0.076; \text{least squares value} = 0.24 \) (Patients with type 2 diabetes were removed from this group.)
- \( \text{Control Group}: n = 209; K_8: \text{mean} = 0.29; \sigma = 0.12 \)
- \( T \text{ test}, P < .0002; F \text{ test}, P < .0001 \)
Eq 25. Guideline: \( TDD = 0.24 \times BWlb \), in which \( K8 \) is rounded from the least squares value
\( TDD: \text{SE} = 12.6; R^2 = 0.4 \)
(Because of space considerations, chart is not shown.)

The details of the \( T \) testing and \( F \) testing are shown in Table 1. For the basal data, the mean of the \( K \) constant is indistinguishable between the 2 groups, but the \( F \) test shows a significant difference in the standard deviation. The interpretation is that for the basal data, the test group is in the center of the entire database and is more tightly grouped.

DISCUSSION

Competing Models for CIR: the 400/500 Rule Versus the 2.8 Rule of the AIM System

As shown in the foregoing material, the 2.8 rule of the AIM system assumes that glucose metabolized per day is proportional to body weight. The 400/500 rule assumes that glucose metabolized per day is the same for everyone.

The AIM assumption is more compatible with the physical principle that it requires more energy to move a large body.

For a statistical comparison of 2 of these systems, the same database must be used, inasmuch as the constants are “best-fit” correlations. We recorrelated the 400/500 rule with our data to obtain a “441 rule” for statistical comparison of the models only (we are not recommending this for clinical use). The AIM system’s 2.8 rule (Fig. 1 C) shows a better \( R^2 \) than the 441 rule (Fig. 1 D). Moreover, the standard error of the quantity \( 1/TDD \) (common to both) is smaller with the AIM 2.8 rule.

The clinicians who advocate the 400/500 rule for CIR do not use its “partner” equation 16 for CF but rather use the AIM-based 1,700 rule, equation 9. The 400/500 rule and the 1,700 rule are established on exactly the same mathematical model, but they are for estimating 2 considerably different variables. The problems can be seen in the units. The units for CF are mg/dL per unit of insulin. The units for CIR are grams per unit of insulin. The appearance of deciliters in the CF is because blood glucose is mea-
sured as a volumetric concentration in the body. This is fundamentally different from the meal-related insulin calculation, which involves carbohydrate grams, counted before consumption and dilution in the body. Therefore, the mathematical models for the 2 factors should not be the same. This use of “mixed systems” should be avoided.

Competing Models: AIM System Versus Solely Weight-Based System

The weight-based system does not use TDD or any other insulin variable as input. Thus, the weight-based system implies that the response to insulin at the cellular level is the same for everyone and that the patient’s dosing calculations with use of this system are nothing more than dilution calculations depending solely on the volume of the body. Nevertheless, current opinions (9,10) suggest that cellular response to insulin varies widely among patients.

If an AIM-using practitioner has a special need for solely weight-based guidelines—for instance, at the initiation of insulin use for a patient when no TDD is available—then the weight-based AIM guideline for TDD (equation 12) can be substituted into the other AIM guidelines. This has the effect of assuming that the patient has type 1 diabetes.

The clinicians who advocate the weight-based system do not generally use equation 20 but rather use equation 21, which was obtained from the 400/500 rule. This causes the weight-based system to inherit the inconsistencies of the 400/500 rule system; the resulting 2 guidelines approximate 2 different variables but with the same mathematical model.

CONCLUSION

This study provides a method of comparing guidelines and developing new guidelines. Among the various systems, the AIM system provides a balance of accuracy against the opposing benefits of being short, easy to remember, and easy to use, in order to minimize dosing errors.

Theoretically, the TDD-based AIM formulas should apply to patients with type 1 diabetes or insulin-deficient type 2 diabetes. The correlation for body weight versus TDD is only for patients with type 1 diabetes. Because only 1 patient with type 2 diabetes was in the data, we recommend the entire AIM system only for patients with type 1 diabetes.

In the current study, the low P values show an association between use of the AIM system and low A1C. There is no study effect because the patients did not know that they were in a study. Furthermore, there is no self-selection because the patients were being adjusted at each visit, not by guidelines but by titration. In view of the fact that an equally valid study could be designed that would assign CFs and CIRs randomly or equally spaced on a scale, instead of by titration, the current study can be viewed as a randomized controlled trial. Additionally, the current study was able to calculate the correlation constants.

A type of study that excels at calculating correlation constants is one in which directly measured blood glucose values before and after an insulin or glucose dose are collected; then the changes in blood glucose are correlated against the dose size. It is conceded that methods such as continuous monitoring (7,11-14), when used to collect this
type of information in a clinical setting, may result in better raw data than the retrospective data herein. It is foreseen that the best guidelines may be produced by using direct measurements and continuous monitoring to refine the K constants in the AIM system.

DISCLOSURE

The authors have no conflicts of interest to disclose.

REFERENCES