Prandial insulin dosing using run-to-run control: application of clinical data and medical expertise to define a suitable performance metric

Received for publication 20 October 2006 and accepted in revised form 31 January 2007.

Running title: Insulin dosing using run-to-run control

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OBJECTIVE: We propose a novel algorithm to adjust prandial insulin dose using sparse blood glucose measurements. The dose is adjusted based on a performance measure for the same meal on the previous day. We determine the best performance measure and tune the algorithm to match the recommendations of experienced physicians.

RESEARCH DESIGN AND METHODS: Eleven subjects with type 1 diabetes mellitus, using CSII, were recruited (7F/4M, age 21–65 years, glycated hemoglobin of 7.1±1.3%). Basal insulin infusion rates were optimized. Target carbohydrate content for the lunch meal was calculated based on a weight maintenance diet. Over a period of 2-4 days subjects were asked to measure their blood glucose according to the algorithm’s protocol. Starting with their usual insulin to carbohydrate ratio, the insulin bolus dose was titrated downward until postprandial glucose levels were high (180–250 mg/dL, 10–14 mmol/L). Subsequently, physicians made insulin bolus recommendations in order to normalize postprandial glucose concentrations. Graphical methods were then used to determine the most appropriate performance measure for the algorithm to match the physician’s decisions. For the best performance measure, the gain of the controller was determined as to best match the dose recommendations of the physicians.

RESULTS: The correlation between the clinically determined dose adjustments and those of the algorithm is $R^2 = 0.95$, $p < 1e-18$.

CONCLUSIONS: We have shown how engineering methods can be melded with medical expertise to develop and refine a dosing algorithm. This algorithm has the potential of drastically simplifying the determination of correct insulin to carbohydrate ratios.
Absolute normalization of blood glucose levels at all times is the ultimate goal of diabetes management. While this remains a point of debate, there is evidence that reducing glycemic variability is an important factor in reducing long-term complications (1, 2). A crucial component of such a strategy is the correct determination of an individual’s insulin to carbohydrate (IC) ratio, defined as the amount of the meal related carbohydrate (in grams) covered by one unit of insulin. The IC ratio is not fixed; it is influenced by a myriad of different factors, such as time of day, levels of physical activity, and psychological and physical stress. Although guidelines exist to select a starting IC ratio, optimizing the insulin dosage is a trial and error process (3–5).

Since the advent of home glucose monitoring, there has been interest in developing algorithms to guide the adjustment of insulin therapy. Skyler et al. (6) and Jovanovic and Peterson (7) were among the first to introduce such heuristic algorithms. Both adjust insulin dosing using rules based on practical experience. The Skyler et al. (6) algorithm uses only preprandial blood glucose measurements, while the Jovanovic and Peterson (7) algorithm uses pre-and postprandial measurements.

Chanoch et al. (8) demonstrated that computer-assisted insulin delivery decision making is feasible. The pocket computer program they tested in five subjects with type 1 diabetes was based on the algorithm proposed by Jovanovic and Peterson (7). In another study Peterson et al. (9) found the approach to be viable. Computer users in this study achieved lower average blood glucose and glycated hemoglobin values, although blood glucose levels were not completely normalized.

Schiffrin et al. (10) saw significant improvements in glycemic control in subjects who used a portable computer programmed to adjust short and intermediate acting insulin dosing. Their algorithm used preprandial blood glucose measurements, and was based on a two-injection per day strategy. Chiarelli et al. (11) compared this method with manual dose adjustment, and although they did not find differences in glycemic control they did observe a reduction in hypoglycemia in the computer users. Peters et al. (12) adapted this algorithm as well, and compared it to manual adjustments. Their conclusion was that metabolic control and safety were comparable.

Beyer et al. (13) created their own algorithms based on the work of Skyler et al. (6). As in the original, only preprandial blood glucose measurements are used. They found that subjects using the computer algorithm did significantly better than the manually adjusted intensive treatment group (14).

None of these studies used the newer rapid-acting insulin analogs. Owens et al. (15) proposed an algorithm that takes advantage of these monomeric insulin formulations, and used a run-to-run control framework adopted from the chemical process industry. The concept was tested in a clinical setting, using blood glucose determinations at 60 and 90 minutes after the start of the meal to adjust the dose and timing of the insulin bolus. The majority of the subjects converged to, or maintained, good glycemic control, but several diverged in their responses (16).

Based on the results from this trial, the run-to-run formulation was modified to overcome the difficulties encountered, such as changing the timing of the insulin bolus with respect to the beginning of the meal and the required fixed timing for the blood glucose determinations (17). The proposed revision to the algorithm adjusts only the dose of the insulin bolus, fixing the timing of the bolus to coincide with the beginning of the meal. The algorithm was tested in silico using the mathematical model proposed by Hovorka et al. (18). Given the uncertainty inherent in any mathematical model, and in particular in the
meal absorption component of the model used, it was imperative that the proposed algorithm metric be tested in vivo. The main purpose of this study was to test and refine, using clinical data, the performance measure used in determining how appropriate the bolus dose is. Medical expertise was also used to tune the controller. The corrections the algorithm would recommend were compared with what an experienced physician would do in the same cases. This study reports our algorithm, using a revised performance measure, is able to match the dose adjustment recommendations of the physicians.

RESEARCH DESIGN AND METHODS

Eleven subjects with type 1 diabetes mellitus were recruited for this study. Inclusion criteria were a diagnosis of type 1 diabetes for at least one year, use of a continuous subcutaneous insulin infusion pump with a rapid-acting insulin analog, and willingness to participate for up to two years. Exclusion criteria included being pregnant or planning on becoming pregnant, being under 18 years of age, unwilling to perform repeated blood glucose measurements, unwilling to take insulin as directed, or having abnormal thyroid, kidney or liver function. There were seven females and four males, with a range of age from 21 to 65 years (43.5±15.6 years, mean±SD), a BMI of 25.5±4.8 kg/m², and glycated hemoglobin of 7.1±1.3%. Duration of diabetes was 16.7±12.5 years (range of 1–39 years). All subjects had undetectable C-peptide levels. The study was approved by the Cottage Health System Office of Research Institutional Review Board, and informed witnessed consent was obtained from all subjects.

Data collection protocol

In order to optimize the basal insulin infusion rates, subjects wore a continuous glucose sensor (CGMS®, Medtronic MiniMed, Inc., Northridge, CA) for a period of three days. On each day they skipped a meal (breakfast one day, lunch the next day, and dinner on the third day) in order to be able to determine basal insulin infusion rates during these meal-time periods, when there are usually prandial insulin boluses present. Using these data, the basal insulin infusion rates were adjusted to a target of 90 mg/dL (5 mmol/L). The process was repeated as necessary until all pre-prandial glucose concentrations were in the target range (19).

Once basal rates were optimized, the subjects were given a target carbohydrate content for their lunch meal based on a weight maintenance diet calculation (adjusted for gender, exercise pattern, and stress level). Lunch was determined to account for 40% of the subject’s calculated total daily caloric requirement, and for carbohydrate to account for 30% of the meal. Total daily caloric requirements were calculated based on weight, gender and activity levels (20). The composition of the meal (beyond the carbohydrate content) was left to the subjects to determine based on their personal preferences.

Subjects were provided with a OneTouch® UltraSmart® blood glucose monitoring system (LifeScan, Inc., Milpitas, CA), which was selected for its memory capacity and its event logging functions. During the baseline period of two to four days subjects were asked to measure their blood glucose according to the protocol the dose adjustment algorithm uses. The subjects all measured their blood glucose at the start of the meal. Two additional postprandial blood glucose determinations were taken: the first one at 60–90 minutes after the start of the meal, the second one at least 30 minutes after the first, but no later than 180 minutes after the start of the meal. On test days, they were asked to start the lunch meal with a blood glucose level within 70–130 mg/dL (3.9–7.2 mmol/L). Starting with their usual IC ratio, their insulin bolus dose was titrated downward until their postprandial glucose levels were high (180–250 mg/dL, 10–14 mmol/L).
Dose adjustment algorithm

The run-to-run algorithm considers each day a “run”. Each meal of the day (i.e. breakfast, lunch and dinner) is adjusted independently. The insulin dosage correction is based on a performance measure (denoted by $\psi$) that quantifies the postprandial glucose excursion as a scalar quantity. The performance measure corresponding to the ideal postprandial response is denoted by $r_{\psi}$. The algorithm then takes the current IC ratio (denoted in the equation below as $v_k$, with the subscript $k$ indicating the current day), and makes an adjustment to calculate the new IC ratio for the next day (denoted as $v_{k+1}$) using

$$v_{k+1} = v_k + K(\psi' - \psi_k)$$

where the gain $K$ is a tuning parameter that determines how aggressive the algorithm is in making a correction. The new IC ratio is used the following day, and the procedure repeated.

In the initial development, the performance measure used is the rate-of-change of blood glucose estimated from the two postprandial blood glucose measurements, and is calculated using

$$\psi_k = \frac{G_2 - G_1}{T_2 - T_1},$$

where $T_1$ and $T_2$ are the minutes elapsed since the beginning of the meal at the time of the first and second postprandial blood glucose measurements ($G_1$ and $G_2$), respectively. This performance measure is further normalized by the carbohydrate content of the meal. Although performance is quite satisfactory in the in silico testing, the glucose absorption from a mixed meal is a weak point of the model used, and therefore required in vivo validation (17).

Data analysis and gain selection

Independently, two physicians skilled in intensified insulin delivery (H. Zisser and L. Jovanović) studied the data sets collected, and made a specific recommendation for each meal as to how the insulin bolus dose should be corrected for the following day. The physicians’ new insulin recommendation was targeted to normalize the postprandial glucose levels the following day, whereas the algorithm could be tuned to converge to the correct IC ratio over a set period of days. The physicians would not make a change to the IC ratio for the following day if the subject’s preprandial glucose concentration was not in the range of 70–120 mg/dL (3.9–6.7 mmol/L). Prandial blood glucose concentrations were excluded from the decision to adjust the IC ratio if they were above or below this target in order to minimize other variables that may impact on the postprandial glucose excursion. The physicians increased the following day’s meal related dosage if either of the two postprandial glucose levels were above 120 mg/dL (6.7 mmol/L). Dosages were increased in a proportional fashion above this level. They would recommend a decrease in the insulin dosage if any of the postprandial glucose levels were below 70 mg/dL (3.9 mmol/L). Additionally, no adjustment to the IC ratio would be made if the first postprandial glucose concentration was above 150 mg/dL (8.3 mmol/L) and the second postprandial glucose level was below 70 mg/dL (3.9 mmol/L); the physicians would recommend instead lowering the total carbohydrate content of the meal for the following day.

Graphical methods were then used to determine if the performance measure proposed from the in silico testing (17) correctly clustered the data points according to the clinical adjustment (increase, decrease or no change to dose). Other possibilities were also considered, including the rate-of-increase in blood glucose in the first phase of the postprandial response (estimated from the pre-meal and first post-meal measurements), the deviations from baseline for the two postprandial determinations, the difference
between the rate-of-increase and the rate-of-decrease, as well as the blood glucose at 60 and 90 minutes from the start of the meal as interpolated from the measured values.

For the performance measure best able to cluster the collected data in accordance to the medical expertise, the gain for the controller was determined as to best match the dose recommendation of the physicians over the full data set.

RESULTS

Of the 43 data sets collected during this portion of the study, only 35 met the pre-meal blood glucose target requirement. For these, the mean pre-meal blood glucose was 98.5±16.9 mg/dL (5.47±0.94 mmol/L). At the first postprandial time-point, which occurred at 74±15 minutes after the start of the meal, mean blood glucose was 133.0±50.7 mg/dL (7.39±2.82 mmol/L). For the second postprandial time-point — at 120±25 minutes after the start of the meal, 47±18 min after the first determination — mean blood glucose was 117.9±30.1 mg/dL (6.55±1.67 mmol/L). For nine of these sets the physicians determined that the insulin bolus dose used was appropriate, thus requiring no change. Another nine required a reduction in the bolus dose, and 17 required that the dose be increased.

The rate of change of blood glucose concentration in the post-prandial period is a common metric physicians look at; this metric was the basis of the original performance measure proposed in (17). Using this performance measure, we found that clustering was impossible to match the clinical decisions (see Figure 1). This is, there is no way to draw boundaries that group and segregate the data points for the three clinical decision categories of increase, decrease or no change of dose. In particular some decisions at 45 and 60 grams of carbohydrate had the same performance measure, but required opposite actions to the insulin dose. Therefore, if this performance measure were used, the algorithm could end up making the wrong decision, increasing the insulin dose when a decrease was needed or vice versa.

Most of the other possibilities tested also fell in this category, with only a few showing the possibility of discrimination. The best of the tested performance measures used the deviation from the preprandial blood glucose at two distinct time points. The first is the deviation at 60 minutes after the start of the meal, which is calculated using the first post-meal blood glucose determination (calculated using the rate-of-change from the pre-meal and first post-meal blood glucose determinations). The second deviation is that at the second post-meal time point. Since the performance measure must be a single scalar value, the distance from the origin to the point defined by the two measures is used. Figure 2 shows these data, together with the regions that determine the action to take based on the performance measure. Mathematically, this is expressed as

\[
G_{60\text{min}} = 60 \cdot \frac{G_1 - G_0}{T_1},
\]

\[
\Delta G_{60\text{min}} = G_{60\text{min}} - G_0,
\]

\[
\Delta G_{T_2} = G_2 - G_0,
\]

\[
\psi = \sqrt{\Delta G_{60\text{min}}^2 + \Delta G_{T_2}^2}
\]

where \(G_0\) is the preprandial blood glucose, \(G_1\) and \(G_2\) are the blood glucose determinations at the first and second postprandial time points (at \(T_1\) and \(T_2\) minutes after the start of the meal), respectively.

The gain for the algorithm was calculated using linear regression to best match the clinically determined dose adjustment. Mathematically, there is no reason for the relationship between the dose adjustment and the performance measure chosen to be linear. Therefore, the dose calculated with the algorithm over the data set was then compared with the clinical determinations (see Figure 3). The correlation
between the two is $R^2 = 0.95, p < 1e-18$. This result confirms that the choice of the linear relationship for the dose adjustment used by the algorithm, together with the performance measure, is satisfactory.

**DISCUSSION**

The reason for selecting the first postprandial blood glucose determination to be at 60 minutes is that, based on previous clinical experience, this is the expected time of the peak glucose excursion. Recent evidence from other studies demonstrates that the actual time-to-peak is closer to 70–75 minutes (21, 22). The actual time to peak will vary, in part due to how closely the insulin bolus dose is matched to the carbohydrate content of the meal. A grossly under-dosed (or missed) bolus will result in the peak being pushed to a later time. The use of the second postprandial measurement was originally conceived to corroborate that indeed the blood glucose had peaked and was on its way back to baseline and not still increasing.

Mathematical models are very useful tools in research and development, but their limitations must be considered in the process. In this case it is known that the glucose absorption from a mixed meal is a weak point of the model, in part because the model is based only on data from liquid oral glucose loads. Given the central role of the meal absorption in relation to insulin dosing it was imperative that the *in silico* results be verified *in vivo*.

To this end, data was gathered according to the desired timing of postprandial blood glucose measurements in relation to the start of the meal. Experienced physicians determined if the insulin bolus dose needed to be increased, kept the same, or decreased. Although the initial performance measure worked well *in silico* testing, it failed to discriminate among the *in vivo* data sets. Different prospective performance measures were tested for their ability to cluster the *in vivo* data in the same way as the experienced physicians.

The best performance measure not only differentiates the clinical data correctly, but it is also intuitive from the physiological standpoint. It uses the blood glucose at 60 minutes as one of the parameters, which is close to the time of the peak blood glucose excursion. Thus too large of a positive deviation from baseline indicates the insulin dose was insufficient.

Certainly penalizing only this excursion can conceivably lead to hypoglycemia due to too strong a dose. Therefore, the deviation at the second postprandial determination from basal serves to balance this effect, and not only to serve as confirmation that the blood glucose has indeed peaked. It is expected that at this point the blood glucose will be close to the baseline value when we have the perfect bolus dose.

In Figure 2 there is a single point in the upper-left quadrant; in this case the meal had 70 g carbohydrate and the bolus administered was 6.5 U of insulin. Before the meal the blood glucose was at 115 mg/dL (6.4 mmol/L), at 85 minutes after the start of the meal it was at 202 mg/dL (11.2 mmol/L), and at 175 minutes it was 85 mg/dL (4.7 mmol/L). The clinical decision was to increase the dose by 0.5 U. Although safe to make this small adjustment, this is very close to the point where an increase could be dangerous. To avoid such a possibility dose changes can be overruled if the blood glucose difference between the second postprandial and the baseline is less than $-10$ mg/dL ($-0.56$ mmol/L). Other such safety checks are easily implemented as well.

The gain of the controller was calculated as to best match the clinical recommendation. Using this gain the correlation between the algorithm’s dose recommendation and that of the physician is very high. For safety, this gain can also be “de-tuned” (i.e. scaled back) so that its
recommendations are not as aggressive as the physician’s, who will generally have additional information to consider when making dose adjustments.

The resulting algorithm, with the defined regions determining the action to take based on simple linear rules, is similar to the concept of parametric programming (23). Such a structure has the advantage of making it possible to exhaustively test all possible actions by the algorithm a priori. The resulting algorithm also suggests that the underlying behavior may be low order (i.e. simple dynamics), which has other implications that could influence more complex algorithms such as those developed for an artificial β-cell.

We have shown how traditional methods from engineering can be melded with medical expertise to develop and refine a dosing algorithm. Given how well the algorithm matches the clinical decisions using only sparse blood glucose measurements bodes well that a new tool could soon be made available that will simplify the current trial and error method of determining the correct insulin-to-carbohydrate ratios.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health, grants R01-DK068706 and R01-DK068663. We would also like to thank Medtronic MiniMed, Inc. and LifeScan, Inc. for their generous support. We also thank all of our subjects for their participation, patience, and support.
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Fig. 1. Distribution of the data points using the original performance measure based on the rate-of-fall of the postprandial blood glucose. Clinical decision of the physicians is denoted as a dose increase (upward pointing triangle), dose unchanged (circles) or a dose decrease (downward pointing triangle). A negative rate indicates blood glucose was still rising at the second postprandial blood glucose determination. There is no way to draw boundaries that group and segregate all the data points for each clinical decision category, thus the measure cannot discriminate accordingly.
Fig. 2. Clustering of data when using the estimated blood glucose at 60 minutes postprandial and the differential between the baseline and final blood glucose levels. Clinical decision of the physicians is denoted as a dose increase (upward pointing triangle), dose unchanged (circles) or a dose decrease (downward pointing triangle). Center box (no hatch marks) indicates desired region corresponding to no dose change, upper-right region (positive slope hatch marks) corresponds to dose increase, and the lower-left region (negative slope hatch marks) to a dose decrease.
Fig. 3. Comparison of the new dose as determined by the algorithm (using the gain derived from the clinical data) and the physician. $R^2 = 0.95$, $p < 1 \times 10^{-18}$. 