# Confusion Regarding Duration of Insulin Action: A Potential Source for Major Insulin Dose Errors by Bolus Calculators

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**John Walsh, PA, CDTC[1], Ruth Roberts, MA[2], and Lutz Heinemann, PhD[3]**

## Abstract

People with diabetes on insulin pumps often use a bolus calculator (BC) to obtain insulin dose recommendations. After the first bolus of the day, residual insulin activity, called bolus insulin on board (BOB), must be correctly accounted for to reduce the size of subsequent boluses and minimize the insulin stacking that would otherwise occur. Critical to achieving this calculation is having an appropriate duration of insulin action (DIA) setting in the BC. Unfortunately, the widespread use of inappropriately short DIAs may be causing unrecognized "stacking" of insulin that leads to unexplained hypoglycemic events. Currently, there is no widely accepted definition or value of the DIA for use in a BC. Various shortcomings regarding the selection of an appropriate DIA setting have led to considerable confusion among clinicians and insulin pump users about this important concept. Traditional pharmacological studies used to determine the pharmacodynamic (PD) properties of rapid-acting insulins create a misleading impression that insulin action times (IATs) in daily life vary from 3 to 5 hours and cause IATs to appear more variable than they actually are. These IAT time ranges are not appropriate for use as the DIA time value required to obtain an accurate bolus recommendation from a BC. We highlight the problems that arise when an inappropriately short DIA leads to excessive bolus recommendations, provide a research protocol to accurately measure DIA, and suggest appropriate DIA time recommendations for use in current clinical practice.

## Keywords

duration of insulin action, insulin therapy, insulin pumps, insulin action time, pharmacodynamics, pharmacokinetics, rapid acting insulin analogs

Modern insulin pumps assist wearers in achieving their metabolic goal of an optimal A1c with low glycemic variability. When basal/bolus therapy is used in insulin-requiring patients, administration of basal insulin by insulin pumps or with syringes averages 48% to 54% of the total daily insulin dose (TDD) with interindividual variation.[1-3] Basal insulin's role is to maintain a steady glycemia in the fasting state.

A pump's bolus calculator (BC) assists with the more complex bolus dose calculations that a user encounters in daily life when it comes to determination of bolus insulin doses.[4] A BC's role is to support the user by recommending adequate bolus doses needed to balance carbohydrate (carb), fat, and protein intake (often simplified as carb counting), and to correct episodes of hyperglycemia. Bolus doses are frequently taken within a few hours of each other while prior insulin boluses retain a substantial degree of glucose-lowering activity. This activity, measured as bolus insulin on board (BOB or IOB) typically lasts more than 5 hours with today's rapid-acting insulin analogs.[5-10] For example, in Mudaliar and colleagues' clamp study of insulin aspart (0.2 U/kg), on which the curvilinear decline in rapid-acting insulin activity was largely based, about 40% of aspart's activity remained at 3 hours following an abdominal injection.[11]

BOB, measured in units of insulin, is monitored through the day by the BC to account for the residual glucose-lowering activity from prior boluses to avoid insulin stacking that would otherwise begin after the first bolus of the day. The accuracy of a pump's duration of insulin action (DIA) setting is critical for assessing the number of units of BOB and appropriately reducing the size of the next bolus dose. Regardless of the duration over which a bolus or injection will lower the glucose, the BC uses the DIA value entered to calculate residual insulin or BOB.

[1]Advanced Metabolic Care + Research, Escondido, CA, USA
[2]Diabetes Services, Inc, San Diego, CA, USA
[3]Science & Co, Düsseldorf, Germany

**Corresponding Author:**
John Walsh, PA, Advanced Metabolic Care + Research, 700 West El Norte Pkwy, Escondido, CA 92026, USA.
Email: jwalsh@amcrclinic.com

Many pump wearers and clinicians have a poor understanding of the importance of the DIA and have an erroneous idea of the best DIA to use. Pharmaceutical research results published in insulin product handouts often refer to a time range for insulin action as 3 to 5 hours. Entering a DIA time as a BC setting that is too short such as 3 hours can hide insulin stacking and lead to hypoglycemic events that are then compensated for by incorrectly adjusting other pump settings. All of this can limit the accuracy of BC bolus recommendations. A number of daily circumstances can cause BOB to become relatively excessive, such as after multiple boluses have been given, when but not all carbs are consumed in a meal, when a meal bolus was forgotten but is then compensated for with the meal bolus and a correction bolus, following increased physical activity, or when a larger-than-needed carb or correction bolus is given in error or given intentionally to quickly lower an elevated glucose.

One study found that 64% of all pump boluses are given less than 4.5 hours after the previous bolus.[12] Another study found that the average number of carbs and correction boluses was 4.14 and 2.12 per day, respectively, during a 10-week period of pump wear among 396 pump wearers.[2] Pump data downloaded from 100 adolescents in Australia found a similar daily bolus frequency of 6.1 per day.[13] Time intervals between boluses from this study would average between 2.95 to 3.93 hours if boluses were given during an 18-hour daytime period or during the entire 24-hour day, respectively. These data suggest that insulin stacking is common and that at least two-thirds of all boluses involve some degree of stacking. Unfortunately, no research to our awareness has focused on the short-term or long-term metabolic outcomes that may result from insulin stacking generated by inappropriate DIA times.

It is worth noting that each insulin pump manufacturer uses a unique configuration for their BC.[14] It is beyond the scope of this article to analyze how these BCs differ in respect to the bolus calculations derived once a DIA time is utilized to determine BOB. Clearly, this topic may also be of interest from a clinical point of view. Of note, BCs are also being used in increasing numbers in Europe within blood glucose systems (Freestyle Insulinx® from Abbott and Accu-Chek® Aviva Expert from Roche) and worldwide in applets by people who are on multiple daily injections.

## DIA Versus IAT

Many factors impact glucose outcomes, so it is always important for clinicians to eliminate any error that contributes to swings in glycemia. Much of the confusion regarding DIA stems from the lack of clear and widely accepted definitions for the terms used to describe insulin action times. Many researchers and clinicians are aware of the terms derived from glucose clamp studies that describe the pharmacodynamic (PD) properties of insulin formulations. In such studies, the infusion rate of an intravenous glucose infusion (GIR, mg/kg/min) is varied so that it counterbalances the metabolic effect induced by an injection of a test insulin.

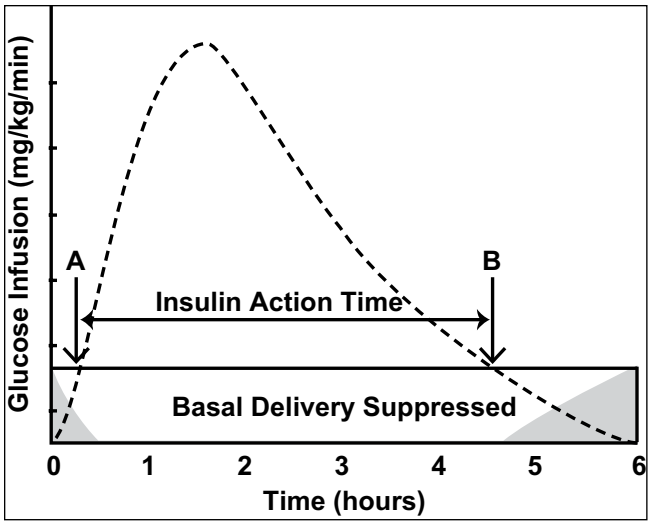


**Figure 1.** Insulin action time (IAT). IAT is measured between points A and B. The method used to measure IAT involves suppression of basal delivery.

The graphical representation of the glucose infusion over time represents the time-action profile of a given insulin formulation. Once a test insulin is injected, as shown in Figure 1, insulin action time (IAT) begins at the first measurable rise in the glucose infusion at point A and ends when the glucose infusion rate returns to baseline at point B. For example, the IAT between points A and B in Figure 1 would be just over 4 hours. IAT times are often quoted as being "3 to 5 hours" for rapid-acting insulins.[15] Measured in this way, IATs are useful for comparing insulins with each other but do not represent the DIA times needed to avoid insulin stacking in a BC.

In glucose clamp studies, the GIR needed to keep the blood glucose constant at a desired target level is measured in healthy subjects or subjects with type 1 diabetes after they receive a single injection of a given insulin formulation.[16] In subjects with type 1 diabetes, an IV insulin infusion is traditionally delivered overnight or for several hours prior to the time when the test insulin is applied to bring glycemia to the target level, for example, 90 mg/dl (5 mmol/L). The IV insulin infusion is suspended shortly before or at the time that a dose of the test insulin is administered; it might even be continued for a while in case of a long-acting test insulin. Under any of these circumstances, the injected test dose covers the functions of both basal and bolus insulin.

In contrast to IAT, the commonly understood definition of DIA in daily life is the time from the injection of the test insulin at point C until the entire metabolic effect of the test insulin has ended as shown be the end of the glucose infusion at point D in Figure 2, while the correct amount of basal insulin is simultaneously delivered from injections of long-acting insulin or infusion of basal insulin from an insulin pump.

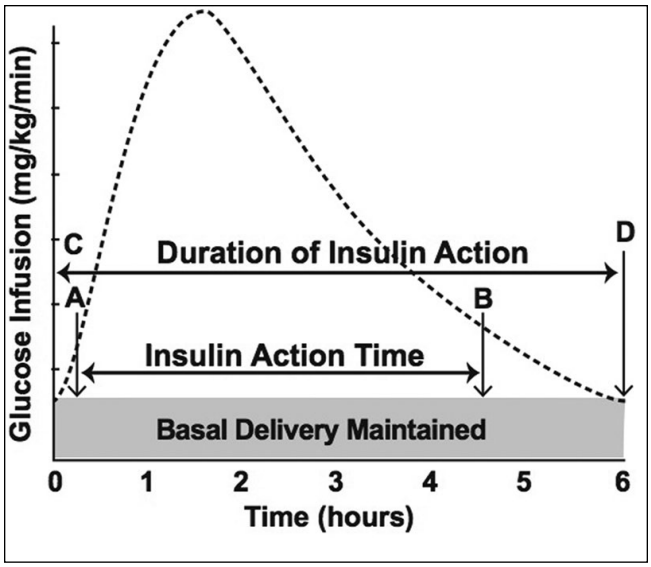


**Figure 2.** Duration of insulin action (DIA). DIA is measured between points C and D. Once basal delivery is maintained, the pharmacodynamic of a bolus insulin can be directly measured.

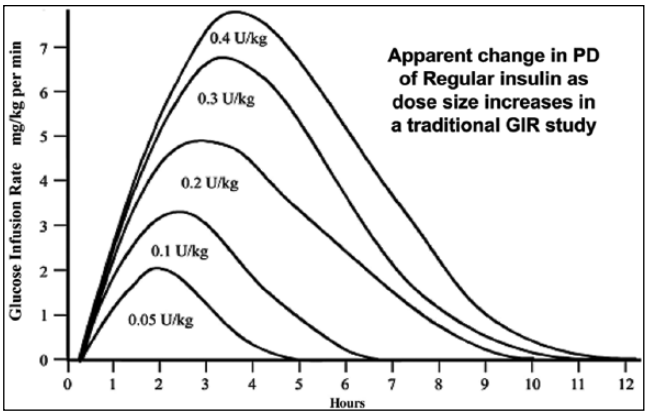


**Figure 3.** Different dose sizes appear to change pharmacodynamics.
Source: Adapted from Heinemann L, Woodworth JR. Insulin lispro; chapter III: pharmacokinetics and metabolism of insulin lispro. *Drugs Today*. 1998;34(suppl C):23-36.

This last aspect is important because glucose clamp studies do not provide the normal basal insulin coverage during the time that the PD properties of a rapid-acting insulin are measured.

In conducting a glucose clamp study, the quantitative determination of the 2 time points needed to calculate the IAT is difficult because there are no criteria to clearly pinpoint the exact time point when GIR increases above baseline or declines back to it. Statistical methods are used to smooth and reduce these fluctuations and provide a more precise determination of the time points when the metabolic effect starts and ends. A sample size of 20 to 30 subjects is required to obtain reliable values for the PD parameters of interest.[16] Maintenance of basal insulin delivery should give more realistic values for DIA and IAT.

In essence, IAT starts later and ends earlier than DIA, that is, the IAT time from clamp studies is shorter than the DIA time. If basal insulin delivery were maintained during clamp studies, the DIA in Figure 2 would be closer to 6 hours compared to the IAT of just over 4 hours in Figure 1. Using data from clamp studies of today's pump insulins when larger doses were studied, the best time estimates for DIA appear to be 5 to 6 hours for most bolus insulin doses.[5-10]

## Insulin Variability May Be Magnified by Current Clamp Studies

In glucose clamp studies, different doses of the test insulin, such as 0.05 to 0.3 or 0.4 U/kg are given to test subjects in an attempt to determine how the IAT varies as the size of test doses is increased. From such studies, it appears as if IAT times increase as insulin doses become larger.[17] Unfortunately, the glucose clamp methodology employed can make these time differences appear more variable than they actually are.[18] For example, Figure 3 displays the time-action profiles of regular human insulin as the dose size is increased from 0.05 to 0.4 U/kg. The respective PD parameters in the figure indicates that IAT lengthens as the dose size increases. However, the coverage of both basal and bolus insulin requirements by the test insulin during such clamp studies does not replicate multiple daily injections (MDI) or insulin pump therapy where basal insulin needs are maintained through alternate insulin doses.

For example, if a 70 kg person is given a dose of 0.05 U/kg in a clamp study, this dose totals 3.5 U. The dose size increases to 21 U when a larger dose of 0.3 U/kg is given. These test doses can be contrasted with the basal requirement of a 70 kg patient with type 1 diabetes that would be expected to be at least 0.8 U/hr, or 4 units over the first 5 hours of a clamp study. For the 3.5 U test dose, a larger percentage of the dose gets diverted toward suppression of hepatic glucose production (HGP) and basal insulin secretion in healthy subjects or toward replacement of basal insulin in subjects with type 1 diabetes than will occur with a 21 U (0.3 U/kg) dose.

Any diversion of the injected test insulin toward suppression of HGP will significantly shorten the apparent IAT of a smaller (U/kg) dose relative to that of a larger dose because the GIR returns to baseline sooner than it would if basal insulin delivery were being maintained. Although rapid-acting insulins appear to have an intraindividual variability (expressed as coefficient of variation) of 20% to 30% in PD measurements,[19] much of this variability may be secondary to a greater diversion of smaller insulin doses toward suppression of HGP. Also, suppression of hepatic gluconeogenesis is inherently more variable than the suppression of basal insulin output from the pancreas.[20,21] Only doses of 0.2 to 0.3 U/kg of a rapid-acting insulin will completely suppress HGP.

Even though the maintenance of basal insulin delivery will complicate the assessment of clamp parameters, we hypothesize that differences in DIA times would be shortened between smaller and larger insulin doses when basal delivery is maintained. This may reduce the intra- and interindividual variability of rapid-acting insulin that is seen in current glucose clamp studies. However, it should be noted that daily life factors like activity and ambient temperature can intermittently shorten or lengthen insulin absorption beyond that seen in clamp experiments where subjects remain at a constant temperature in a supine position. So in daily life, insulin variability might be higher than under controlled conditions.

## Why Do Clinicians and Patients Use Inappropriately Short DIA Times?

Pump users have no intuitive basis on which to select an appropriate DIA. Personal experience often reinforces the belief that insulin works faster than it really does. For example, it seems logical to blame the bolus just given when a low blood glucose occurs an hour or so after a meal, rather than the BOB that was still active from a bolus given a few hours earlier. It is also easy to misinterpret an excessive bolus dose as very fast insulin action.

The most common error in DIA times by patients and clinicians is to select a DIA that is too short. In an online discussion, pump wearers were asked what DIA setting they were using. Nineteen respondents reported a median DIA time of 3 hours and an average time of 3.4 hours, with a range between 2.5 and 5 hours.[22]

A common belief among parents of children with diabetes and the physicians who care for them is that with the small insulin doses used by younger children will have a DIA of approximately 3 hours.[23] However, bolus dose sizes in U/kg body weight are similar between children and adults with type 1 diabetes. PD studies in children aged 3.5 to 6.9 years old show a persistent insulin activity for at least 5 hours following a bolus of a rapid-acting insulin analog, with no significant differences in PD between children and adults.[15,23-25] Use of an inappropriately short DIA time of 3 hours in a BC makes insulin stacking especially common in children who tend to bolus more frequently.

Many patients (and physicians) mistakenly believe that DIA is the same as the pharmacokinetics (PK) of insulin formulations found in product handouts rather than their induced PD effect. It is important to understand that even when the levels of insulin circulating in the blood stream (PK) have declined back to baseline, its metabolic effect continues for some hours afterward (PD).

Most insulin pump manufacturers have selected default times for the DIA of 4 or 6 hours for their pump, but it is not clear why they allow options for DIA times to range between 2 and 8 hours, a range that is far wider than the times suitable for current pump insulins. The logic for the inclusion of DIA time choices of 2 or 3 hours is unclear, although longer times of 7 and 8 hours may be appropriate for regular U-100 and higher concentration insulins. These shorter DIA times also appear unlikely to apply to the ultrarapid prandial insulins that are currently in clinical studies.

Patients and some clinicians may presume that the availability of this wide range of DIA times indicates that all are appropriate choices or that the selection of a DIA time is arbitrary. What it actually indicates is that there is no agreed-on standard for DIA. The end result, unfortunately, is that many patients and clinicians enter inappropriately short DIA values into insulin pumps.

## Problematic Adjustments That Arise When a Short DIA Is Used

Many patients and clinicians do not appear to realize how dramatically changes in the DIA setting can affect the size of subsequent bolus recommendations. If a BC is recommending bolus doses that are too small due to an incorrect carb factor setting, some pump wearers will shorten their DIA time to obtain larger bolus doses rather than address the real reason for a persistent insulin deficit by lowering the carb factor (insulin to carb ratio) or counting carbs more accurately.

When a DIA time is chosen that is shorter than insulin's metabolic activity, a significant amount of residual bolus insulin activity may be hidden from the pump wearer. As noted above, some 40% of the glucose-lowering effect of insulin aspart (0.2 U/kg) may remain at 3 hours.[11] Table 1 shows how the estimated units of residual BOB increase when a DIA of 3 hours is increased to more realistic values. The first column shows DIA time selections available in many BCs. The second column shows the units of BOB that the BC calculates to remain active 3 hours after a 10 U bolus for this DIA time. If a DIA time of 3 hours is selected, no BOB appears to be active at 3 hours following a 10 U bolus, so the BC will recommend full bolus coverage for any carb intake or high glucose at that time. However, when more realistic times of 4.5 to 6.0 hours are selected, the BC will calculate that 2.5 to 4.7 units of glucose-lowering activity remain at 3 hours. The excessive correction bolus that results from a DIA of 3 hours will lead to hypoglycemia if other BC settings have been correctly set. The hypoglycemic events that ensue from a short DIA time selection may be blamed on the basal rates, carb factor, or correction factor and lead to inappropriate adjustments in these settings. Selection of an inappropriately short DIA time complicates the pump wearer's path toward better metabolic control.

Short DIA times become a more serious clinical issue for those who attempt to keep their glucose near a euglycemic range. Although clinical experience suggests that hidden insulin stacking caused by short DIA times is a common cause for unexplained hypoglycemia, we are unaware of any research into this area. Clinical experiments or clinical data analysis focused on DIA times would help to better understand this therapeutic issue.

**Table 1.** Impact of DIA settings in hours on the insulin dose in units that the BG believes is still active after 3 hours.

| When the DIA timesetting is: | The BC will calculate this many units of insulin remain 3 hrs after a 10U bolus: |
|---|---|
| 3.0 hrs | 0.0 U |
| 4.0 hrs | 1.8 U |
| 4.5 hrs | 2.5 U |
| 5.0 hrs | 3.3 U |
| 5.5 hrs | 4.0 U |
| 6.0 hrs | 4.7 U |

## Additional Considerations for BCs

An accurate DIA is required for the pump BC to make appropriate bolus recommendations. It is worthwhile to note that considerable differences can be found in bolus dose recommendations given by different BCs, even with identical DIA time settings and identical BOB values at the time a bolus is given. Beyond avoidance of insulin stacking, tracking of their BOB allows pump users to compare a recent capillary blood glucose measurement (including trend information when a continuous glucose monitor [CGM] is worn) with their BOB to determine whether they need a correction bolus or additional carbs.

For about 90 to 120 minutes following a meal bolus, a BC cannot accurately calculate the counteracting impact from a bolus that is starting to lower glycemia against the increase in glycemia generated by meal carbs being absorbed from the gut into the bloodstream. After this time, carb absorption from most meals has completed and will have little further impact on glycemia[26]; the current BOB can be compared with the glucose result to determine whether an insulin or a carb deficit may be present.

For example, Figure 4 shows a glucose measurement 2 hours after a meal, beyond the blind spot for most meals. Line A in the figure shows a slow decline in the glucose level where the BOB will not be sufficient to lower the glucose level toward the target value. Here, a correction bolus is needed. Line B shows BOB that is well balanced with the current glucose level. Line C shows excessive BOB that is likely to require carb intake or a reduction in a planned carb bolus.

Pump users can better maintain euglycemia and plan their physical activity when they are aware of their current BOB and glucose level. These minimal data provide optimal guidance for users' subsequent actions once other pump settings have been reasonably optimized.

## Limits of Existing IAT and DIA Research

Current experimental clamp study designs do not replicate normal life with diabetes since test subjects lay in bed with minimal physical activity. Daily factors such as activity level,

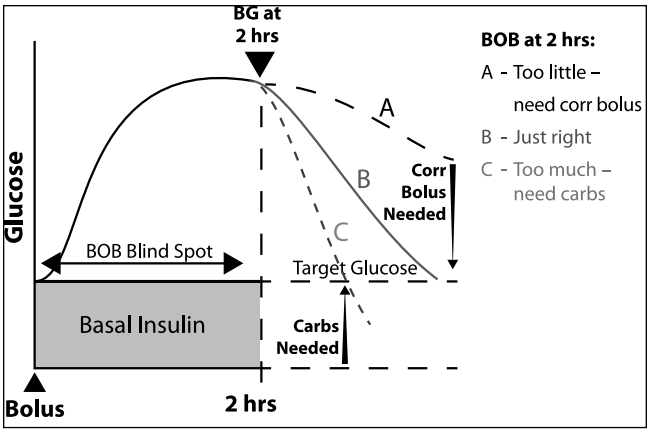


**Figure 4.** Bolus on board at 2 hours: Too little, much, or just right. The figure shows a glucose reading 2 hours after a carb bolus when most meals will have little further impact on the glucose. This glucose can be compared with the bolus insulin on board or units of glucose-lowering activity at that time to evaluate whether a correction bolus is needed or carb intake may be needed now or later.

stress, illness, and food-related effects on insulin action can all affect blood glucose levels over time. Other factors, such as the following, may have a more direct impact on DIA times:

- Bolus type (regular, combination, extended)
- Length of infusion set wear
- Anatomic location for insulin delivery (longer to shorter DIA times in the thigh, arm, abdomen, respectively)[27]
- Insulin infusion near exercising muscles (hastens insulin's metabolic effect in arm and thigh sites)
- Insulin resistance in type 1 or type 2 diabetes that require correspondingly larger (U/kg) insulin doses can delay insulin action
- Other factors such as BMI, age, medications, and ambient temperature that also affect blood flow and insulin absorption

These factors might help to explain perceived or actual differences that arise between the data determined under glucose clamp conditions and those observed in daily life.

Designing and conducting glucose clamp studies that provide reliable data require a certain amount of experience. Despite inherent limitations of the glucose clamp technique, a summary of the outcome of a series of glucose clamp studies with a variety of different insulin formulations while using a relatively standardized automated glucose clamp technique at a single research center provides a good source for the PD properties of the 3 rapid-acting insulin analogs used in insulin pump therapy (Table 2).[28] Late $t_{50\%}$ times, when insulin action has declined to 50% from the peak, were available for 4 experiments from 3 studies that used 12 units

**Table 2.** Pharmacokinetic/Pharmacodynamic Characteristics of Prandial Insulins Used in Pumps From Studies Done at One Research Center with subcutaneous insulin injection.

| | | | Insulin exposure (PK, min) | Insulin action (GIR, min) | | |
|---|---|---|---|---|---|---|
| Reference | Population (N) | Dose | Peak ($t_{max}$) | Onset (early $t_{50\%}$) | Peak ($t_{max}$) | Offset (late $t_{50\%}$) |
| Lispro | | | | | | |
| Rave 2005 (9) | Healthy (17) | 18 U | 148 | 41 | 137 | 313 |
| Rave 2005 (10) | Healthy (20) | 18 U | 45 | 38 | 136 | 273 |
| Rave 2005 (10) | Healthy (20) | 12 U | 45 | 38 | 112 | 248 |
| Rave 2005 (10) | Healthy (20) | 6 U | 45 | 35 | 85 | |
| Heise 2007 (32) | Healthy (80) | 0.2 U/kg | 76 | | 171 | |
| Heise 2007 (32) | Healthy (80) | 0.4 U/kg | 92 | | 198 | |
| Becker 2008 (33) | T1DM (not specified) | 0.2 U/kg | 58 | 46 | 94 | |
| Aspart | | | | | | |
| Heinemann 1998 (6) | Healthy (10) | 0.2 U/kg | 70 | 41 | 104 | 264 |
| Heinemann 1998 (6) | Healthy (10) | 0.2 U/kg | 48 | | 104 | |
| Glulisine | | | | | | |
| Becker 2008 (33) | T1DM (18) | 0.15 U/kg | 57 | | 114 | |
| Becker 2008 (33) | T1DM (not specified) | 0.2 U/kg | 51 | 34 | 98 | |
| Becker 2008 (33) | Healthy (not specified) | 0.1 U/kg | 44 | 31 | 127 | |
| Heise 2007 (32) | Healthy (80) | 0.2 U/kg | 94 | | 190 | |
| Heise 2007 (32) | Healthy (80) | 0.4 U/kg | 100 | | 196 | |
| Mean | | | 69.5 | 38.0 | 133.3 | 274.5 |
| SD | | | 30.1 | 4.7 | 39.7 | 27.7 |

to 0.3 U/kg (approximately 0.18 to 0.3 U/kg) of insulin. The late $t_{50\%}$ times in these experiments averaged 4 hours and 34 minutes (274.5 minutes). These data suggest that DIA times, although not directly measured, appear to be over 5 hours in duration when assessed in glucose clamp trials.

## Experimental Protocol to Estimate DIA in Patients With Type 1 Diabetes

DIA times for MDI or pump patients have never been directly researched to determine appropriate values. The experimental clamp protocol outlined below may allow more precise measurement of the DIA times for rapid-acting insulins. During testing, it is important that basal insulin delivery is maintained at therapeutic levels in patients with type 1 diabetes (subcutaneous [SC] injection of a long-acting insulin or basal insulin delivery from an insulin pump) before the test insulin is applied.

## Experimental Study Design

1. Activities of the study participants on the days prior to the experimental study days should be standardized to ensure that physical activity, alcohol intake, and other factors that could affect the study outcome are similar on all "prestudy days."
2. Basal insulin needs of each enrolled C-peptide-negative subject with type 1 diabetes should be evaluated carefully prior to the study days. Subjects selected for this study should be in relatively good control (A1c less than 7.5% without frequent hypoglycemia) to minimize any impact from insulin resistance associated with hyperglycemia.
3. On the study days, regular insulin can be infused SC by an insulin pump to maintain basal insulin coverage, while a rapid-acting insulin is applied by injection or by infusion from a second pump to determine its DIA. The catheter used for these infusions should be inserted for more than 12 hours and kept open with a low-dose infusion. This procedure allows the PK properties of each rapid-acting insulin to be determined with a specific assay device, while retaining identical baseline metabolic effects through use of regular insulin as the basal insulin.[29] Rapid-acting insulins can be alternated as desired.
4. Four different insulin doses (0.05/0.1/0.2/0.3 U/kg) should be tested on different study days to determine how much the concentration of an insulin dose may affect DIA.
5. Experimental study duration should be long enough to allow GIR to decline back to baseline level to fully measure DIA (up to 10 hours).

6. Stable isotopes can be used to evaluate the degree of suppression of HGP throughout these experiments. To reflect normal basal insulin requirements, HGP should be suppressed sufficiently to maintain euglycemia overnight prior to initiation of the study.

This study protocol should provide more realistic DIA times that reflect the actual action times of the insulins commonly used in pumps. Determination of basal insulin requirements in the first step should eliminate some of the variation in insulin sensitivity that inherently exists between different test subjects. It is of note that the doses of basal insulin required in subjects with type 1 diabetes are larger and differ significantly from those of someone with a healthy pancreas. In a healthy person, HGP is directly regulated through the portal vein with less total insulin output and lower levels of peripheral insulin.

To verify optimal DIA settings, the DIA times determined from such glucose clamp studies can be compared with DIA estimates determined from data downloaded from patients wearing pumps and CGM systems. A method to simultaneously test a patient's correction factor and DIA has been described elsewhere.[30] Such an analysis of downloaded pump data may also help determine whether excess hypoglycemia is generated by short DIA times, and whether other pump settings are being adjusted to compensate for any insulin stacking that this generates, such as using higher (weaker) I:C ratios for the meals that follow breakfast.

Variations on this basal/bolus PD methodology would also be of interest. For example, one might verify an optimal basal replacement from pump basal rates or long-acting insulin doses by whether a relatively normal glucose level can be maintained without requiring a glucose infusion. Another example would be to replicate the glucose infusion required to balance the size and timing of an individual's typical daily bolus doses to measure the extent to which insulin stacking occurs in daily life.[31] This may also provide an optimal method to compare the insulin stacking seen with today's bolus insulins with that of the ultrafast insulins that are now in clinical testing. It would be of interest, of course, to determine whether DIA depends more on absolute doses (in U) or body-weight-corrected doses (U/kg).

## Additional Pump and DIA Research

Other research data regarding pump practices, such as the following, would be helpful to evaluate DIA:

- The sizes of bolus insulin doses (U/kg) that are commonly given
- Typical time intervals between bolus doses
- Which anatomic sites are used for infusion sets or patch pumps
- Whether the time required to infuse a large insulin bolus (1 to 15 minutes from different insulin pumps) alters the DIA relative to an injection of insulin[28]
- And, of special interest, the DIA times that are currently being used; if these times differ significantly from research data, this will clarify the impact that the DIA has on the suggested insulin doses under realistic circumstances, that is, to verify how small or big this issue is

To our knowledge, there are limited data regarding these clinically relevant questions, although queries of downloaded pump data could provide useful information relatively easily.

## Recommendations for Selecting DIA Times in Current Practice

Currently, we lack reliable data for DIA. Until respective research studies are performed and such data become available, we suggest the following approach:

1. BC DIA times should not be based on currently published IAT ranges.
2. PD data generated with higher insulin doses (0.2 U/kg or larger) currently provide the best estimates for DIA settings in a pump or BC.
3. Currently, times between 4.5 and 6.5 hours may provide better estimates for the DIA setting. For boluses that are typically larger than 0.2 U/kg, a DIA setting of 6.0 to 6.5 hours may be preferred. These estimates for appropriate DIA time settings may need to be lengthened when more precise DIA measurements become available.
4. When blood glucose readings are often elevated, discourage patients from shortening their DIA to increase the size of bolus doses because this is likely to introduce or enhance errors in other BC settings. When insufficient insulin doses are given, address the insulin deficit directly with higher basal rates or a lower carb factors or correction factors, or encourage a change in bolus habits.

## Conclusions

Widespread confusion exists among clinicians and patients regarding the selection of an accurate DIA setting in a BC. Further confusion exists about how dramatically the DIA setting can affect BOB calculations. It is somewhat disturbing to see how casually patients and clinicians modify a parameter that has a profound impact on their risk of hypoglycemia. Both the importance and accuracy of DIA settings must be clarified to ensure patient safety and success for the large number of people who utilize a BC each day. In this article, we suggest DIA times that may improve safety for those who use a BC to obtain dose recommendations from an insulin pump or with MDI.

Well-designed research studies are needed to directly measure DIA times for today's rapid-acting insulins. Studies should also be performed to evaluate the impact that the

current use of short DIA times may be having on hypoglycemia and glucose variability.

Although faster insulin action is being sought,[28] removal of inappropriate DIA time choices, such as 2 and 3 hours, from insulin pump BCs may allow more accurate tuning of basal rates, carb factors, and correction factors for a significant number of those who use a BC to obtain bolus recommendations. During pump and BC training, the nuances and consequences of all pump settings must be covered, including the DIA.[30] Clinicians and users should be trained regarding a uniform handling of these important aspects of insulin pump therapy. The training should lead to proper alignment of the DIA setting with basal rates, carb factor, and correction factor. If clinicians plan to correct an inappropriately short DIA time, they should be aware that this may require readjustment of other pump settings that may have been altered to accommodate the short DIA time. Use of an accurate DIA becomes more critical as a patient's average glucose approaches an optimal A1c range, since an incorrect calculation of BOB can more quickly cause hypoglycemia. It may be more difficult for someone who uses an inappropriately short DIA to reach such an A1c.

It is paramount that insulin manufacturers verify actual DIA for rapid-acting insulins on the market so that people who use insulin know how to avoid insulin stacking. In addition, insulin pump manufacturers should reach consensus on how to harmonize BC settings between different insulin pumps. It would certainly be worthwhile to establish a round table to discuss such aspects and to involve regulatory authorities and the Diabetes Technology Society, which has been involved in recent activities regarding better accuracy in blood glucose meter systems in the United States. Patient safety requires that immediate steps be taken to measure DIA accurately and to provide easy access to this information to those who use a BC for their bolus recommendations.

## Abbreviations

BC, bolus calculator; BOB, bolus insulin on board; carb, carbohydrate; CGM, continuous glucose monitor; DIA, duration of insulin action; GIR, glucose infusion rate; HGP, hepatic glucose production; IAT, insulin action time; IOB, insulin on board; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous.

## Declaration of Conflicting Interests

JW and RR have no conflict of interest on this research. LH hold shares in the Profil Institute for Metabolic Research, Neuss, Germany, and the Profil Institute for Clinical Research, San Diego, CA. LH and JW are also consultants for a range of companies that develop new diagnostic and therapeutic options for the treatment of diabetes.

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