Clinical Performance of Three Bolus Calculators in Subjects with Type 1 Diabetes Mellitus: A Head-to-Head-to-Head Comparison

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Abstract

Background: Insulin pump systems now provide automated bolus calculators (ABCs) that electronically calculate insulin boluses to address carbohydrate intake and out-of-range blood glucose (bG) levels. We compared the efficacy of three ABCs (Accu-Chek® Combo [Roche Insulin Delivery Systems (IDS), Inc., Fishers, IN, a member of the Roche Group], Animas® 2020 [Animas Corp., West Chester, PA, a Johnson and Johnson company], and MiniMed Paradigm Bolus Wizard® [Medtronic MiniMed, Northridge, CA]) to safely reduce postprandial hyperglycemia in type 1 diabetes mellitus (T1DM).

Methods: T1DM subjects (n = 24) were recruited at a single center for a prospective, triple crossover study. ABCs with the programmed target range (80–140 mg/dL) were used in random order. Postprandial hyperglycemia was induced by reducing the calculated bolus by 25%. Two hours after test meals, the ABCs were allowed to determine whether a correction bolus was needed. Differences between 6-h bG values after test meals that achieved 2-h postprandial hyperglycemia and the mean of the target range (110 mg/dL) were determined.

Results: The mean difference between 6-h bG levels following test meals and the 110 mg/dL bG target with the MiniMed device (47.4 ± 31.8 mg/dL) was significantly higher than the Animas (17.3 ± 30.9 mg/dL) and Roche IDS (18.8 ± 33.8 mg/dL) devices (P = 0.0022 and P = 0.0049, respectively). The number of meals with 2-h postprandial hyperglycemia and bG levels at 2 h was similar. Roche IDS and Animas devices recommended correction boluses significantly more frequently than the MiniMed device. ABC use was not associated with severe hypoglycemia. There was no significant difference in the rate of mild hypoglycemia (bG < 60 mg/dL not requiring assistance) among the three groups (Roche IDS and Animas, n = 2; MiniMed, n = 0).

Conclusions: In this study, the Roche IDS and Animas devices were more efficacious in controlling postprandial hyperglycemia than the MiniMed device. This may be due, in part, to differences in ABC setup protocols and algorithms. Use of ABCs can assist in controlling postprandial glycemia without significant hypoglycemia.

Introduction

Intensive therapeutic management aimed at attaining tight glycemic control is associated with significant reductions in diabetes-related complications.1–3 Insulin pump therapy has become increasingly popular as a means of insulin delivery for individuals with type 1 diabetes (T1DM) and type 2 diabetes.4 Use of insulin pump therapy has been shown to improve glycemic control, reduce hypoglycemia, and improve quality of life.4–10 Accurate insulin dosing is needed to maintain desired overall glycemic control; however, accuracy in prandial insulin dosing is particularly important in light of numerous reports regarding the detrimental relationship between postprandial hyperglycemia and the development/progression of microvascular and macrovascular complications of diabetes.11–15

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A key feature of most insulin delivery systems is the capability to automatically calculate bolus insulin dosages to cover carbohydrate (CHO) intake and address out-of-range blood glucose (bG) levels. Prior to the availability of these automated bolus calculators (ABCs), patients were required to perform complex calculations based upon their target bG, current bG, insulin sensitivity factor (ISF), insulin-to-CHO ratio (I:CHO), and total grams of CHO in each meal/snack in order to determine accurate bolus dosages. Because manual calculation of insulin boluses is complex and time consuming, patients may rely on empirical estimates, which may result in hypoglycemia, hyperglycemia, and weight gain. Furthermore, because manual bolus calculation does not take into account the effect of the active insulin that remains from the initial bolus (insulin-on-board), there is a high potential for errors, particularly when determining a correction bolus.

All current ABCs perform the same basic function; however, there are potentially important differences in the algorithms used to calculate correction boluses. Unless the remaining amount of active insulin is accurately determined, an ABC may tend to under- or over-treat postprandial hyperglycemia. In addition, proprietary differences in correction “rules” can affect the subsequent recommendations for correction boluses. For example, some ABCs correct to the midpoint of the preprogrammed bG target range (depending on whether the bolus is linked with CHO intake), whereas other systems correct to the limits of the target range.

Although results from studies comparing ABC use with nonuse have been described in previous reports, this study is the first prospective, head-to-head comparison of the key differences among three ABCs within a controlled clinical setting.

**Research Design and Methods**

**Study design**

In this single-site, prospective, open, triple crossover, exploratory study, we assessed the efficacy of three ABCs to identify and address postprandial hyperglycemia. The ABCs studied were: (1) Accu-Chek® Combo (Roche Insulin Delivery Systems [Roche IDS], Inc. [formerly Disetronic], Fishers, IN, a member of the Roche Group); (2) Animas® 2020 (Animas Corp., West Chester, PA, a Johnson & Johnson company); and (3) MiniMed Paradigm Bolus Wizard® (Medtronic MiniMed, Northridge, CA). All of the ABCs studied are CE (Conformité Europeenne) marked; the Roche IDS device was not Food and Drug Administration-approved for use in the United States at the time of this study.

The study was conducted at the Institute for Diabetes-Technology at Ulm University, Ulm, Germany, and in accordance with the Declaration of Helsinki and good clinical practice guidelines. All subjects provided written informed consent.

**Subjects**

The study enrolled 24 adult subjects with TIDM who were currently using an insulin pump with rapid-acting analog insulin; all subjects had used an insulin pump for at least 6 months prior to screening. All subjects were white; there were 14 female and 10 male subjects (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Subject Demographics (n = 24)</th>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td>45.5 ± 11.1</td>
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<tr>
<td><strong>Diabetes’ duration (years)</strong></td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
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<tr>
<td><strong>Hemoglobin A1c (%)</strong></td>
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<tr>
<td><strong>Daily basal insulin (U)</strong></td>
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<tr>
<td><strong>Total insulin dose per day (U)</strong></td>
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| **Insulin sensitivity factors (mg/dL/U)** | |
| — | 42.9 ± 13.0 | 39.6 ± 10.0 |
| 04:30–10:30 h | 44.0 ± 16.2 | 44.8 ± 10.7 |
| 15:30–21:30 h | 45.4 ± 15.6 | 41.7 ± 9.9 |
| 21:30–04:30 h | 48.8 ± 21.9 | 55.8 ± 14.7 |

**Insulin-to-carbohydrate ratios (g/U)**

| — | Breakfast | Lunch | Dinner |
| — | 8.8 ± 2.9 | 10.4 ± 3.0 | 9.4 ± 2.8 |
| — | 11.8 ± 3.0 | 13.2 ± 3.2 | 12.4 ± 3.0 |

Data are mean ± SD values.

Exclusion criteria included >9% hemoglobin A1c, severe late complications of diabetes, current addiction to alcohol/substances of abuse, psychological issues that would impair ability to consent/participate, pregnancy or lactation, any known life-threatening disease, intensive physical sport in daily life, or use of steroids of >14 days within the last 3 months.

**Notable differences in ABC devices**

A key difference between the ABCs is the manner in which the Roche IDS device calculates remaining active insulin. Unlike the Animas and MiniMed devices, the Roche IDS device does not consider the glucose centric insulin (insulin given to lower a high bG) is used in the correction dose calculation. Another difference involves the algorithmic “rules” governing correction targets. Whereas the Roche IDS and Animas devices correct to the midpoint of the preprogrammed bG target range, the MiniMed device corrects to the upper or lower limit of the bG target range, respectively (Fig. 1). In this study, the target range was 80–140 mg/dL, which meant that the Roche IDS and Animas devices corrected to 110 mg/dL as a target point; the MiniMed device corrected to 140 mg/dL if bG was above target range.

In addition to these differences, the Roche IDS device required setting of two additional programmable settings unique to its bolus calculator: Meal Rise (level to which bG is allowed to rise after a meal before correction bolus is recommended) and Offset Time (duration of time before insulin begins to significantly lower bG). These parameters and the insulin action time are used to define postprandial bG limits, within which no correction is recommended.

**Protocol**

The study protocol is presented in Figure 2. Subjects underwent 1 day of screening to obtain laboratory measurements, perform physical assessments, and assess and check all needed insulin therapy parameters. Screening was followed by 10–21 days of intensive self-monitoring of bG (SMBG) to
generate data to confirm ISF, I:CHO, total daily dose of insulin, basal rate, and frequency of hypo- and hyperglycemia. The intensive self-monitoring phase included several fasting phases for basal rate tests and to confirm ISF for different times of the day. Subjects were instructed to eat standardized test meals on multiple occasions to confirm I:CHO ratios. Based on these data, the therapy parameters were adjusted by a physician for the course of the study, if needed. Following the intensive SMBG period, subjects returned to the study site to have their insulin parameters rechecked and were assigned to participate in one of six experimental blocks based on the timing of their completion of screening and intensive monitoring activities.

An equal number of subjects were assigned to each block. Each experimental block used one unique order of ABC use combination; all six possible combinations were used to negate any effect the order of ABC use might have on the effectiveness of the individual ABC. All subjects assigned to a given experimental block followed the same “order of ABC use” combination.

For the in-clinic phase, subjects stayed at the investigational site from the afternoon of day 1 until the morning of day 9. On days 1 and 2, a physical examination and laboratory test were performed to recheck the inclusion and exclusion criteria;

FIG. 1. Automated bolus calculator correction rules when bolus recommendation is associated with carbohydrate intake. For the Roche IDS device, the correction within target range only applies if the bolus advice is given in combination with carbohydrate intake. If there are no carbohydrates present, blood glucose values within target range do not prompt corrective action.

FIG. 2. Study protocol. SMBG, self-monitoring of blood glucose.
insulin therapy parameters were rechecked and adjusted if needed. The three bolus calculators were used on days 3–4, 5–6, and 7–8 in random order. Apart from individual subject settings for basal rate, ISF, and 1CHO, insulin therapy parameters were set identically across all three bolus advisors: target range (80–140 mg/dL), hypoglycemia (<60 mg/dL), and insulin acting time (4 h). The Roche IDS ABC has two unique features, Meal Rise and Offset Time, which were set at 75 mg/dL and 75 min, respectively.

During days 3–8, subjects consumed two types of meals: test meals, consisting of 45% CHO, 20% protein, and 35% fat, and compensation meals, consisting of 55% CHO, 15% protein, and 30% fat. Subjects consumed three meals per day, alternating between test meals and compensation meals. Subjects performed light exercise (30-min walk) following the first compensation meal of the day.

Use of each ABC started at midnight. Prior to each meal, the ABC was used to calculate the initial prandial insulin dose needed to cover the anticipated CHO intake based on each subject’s individualized parameters and was allowed to make corrections for out-of-target bG. For test meals, the recommended insulin bolus was reduced by 25% in order to induce postprandial hyperglycemia at 2 h following the meal.

SMBG was performed at 03:00 h and then hourly from 06:00 to 24:00 h during days 3–8. At 2 h following each meal, SMBG results were entered into the ABC to obtain a correction bolus recommendation; recommended correction boluses were administered. In the event that bG levels were >350 mg/dL or remained >250 mg/dL longer than 2 h, additional correction boluses were administered based on the ABC recommendation or at the physician’s discretion. Hypoglycemia, defined as <60 mg/dL during the day, symptomatic at any bG level, or <70 mg/dL during the night, was treated orally with 17 g of Dextropur (Dextro Energy GmbH, Krefeld, Germany) dextrose powder solved in tea, which contains 91% CHO, resulting in 15.5 g of CHO.

**Insulin pump device**

Although the three ABCs were used to calculate bolus doses, all insulin doses were administered using the Accu-Chek Spirit insulin pump and infusion set (Roche IDS) during the in-clinic phase. Subjects used their own brand of analog insulin. Study physicians checked all insulin doses calculated by the ABCs before administration. Every second day, the insulin catheter was changed.

**Standardization of meals**

Clinical staff calculated the composition of CHO, fat, and protein per meal. Meal size was adjusted to meet caloric requirements of each subject; differences of ±5% were considered acceptable. The individual daily calories for each subject was calculated based on World Health Organization 1985 energy and protein requirements, adding additional calories for light activity.

**SMBG**

The bG measurements for the in-clinic phase were performed in duplicate with the Accu-Chek Aviva Combo blood glucose meter (Roche IDS). If duplicate bG values <100 mg/dL differed by more than 10 mg/dL, the tests were repeated. If bG values >100 mg/dL differed by >10%, the tests were repeated.

**Efficacy assessments**

The primary end point of the study was the mean difference by subject between bG values achieved at 6 h after all test meals and the mean value (110 mg/dL) of the target range (80–140 mg/dL), using the three ABCs. In the case of hypoglycemia or hyperglycemia intervention, the corresponding bG value at the time of the intervention was carried forward and used as the reported 6-h bG. A subject had to have two out of three usable test meals per ABC for the data to be included in the analysis.

Additional end points, which were evaluated by single meals, included (1) number of test meals achieving bG target range at 6 h following the test meal after receiving a bolus recommendation, (2) differences in recommended correction bolus dosages when 2-h postprandial bG is >140 mg/dL, (3) the amount of time a subject stays within the bG target range during the period managed by each ABC, (4) the rate of occurrence of hypoglycemia 6 h following the meal (postprandial phase), and (5) the overall rate of hypoglycemia during the test phase of the study.

**Safety assessments**

Safety assessments categorized adverse events (AEs) as either anticipated or unanticipated. Anticipated AEs that pose minimal immediate risk to study subjects were not tracked and logged as AEs. All significant anticipated AEs and unanticipated AEs as well as unanticipated adverse device effects were documented. Severe hypoglycemia was defined as a hypoglycemic event during which the person required the assistance of another person. All hypoglycemia episodes that occurred during the course of the study were documented.

**Statistical analysis**

For the primary end point, a three-sample comparison between all devices was performed by means of an analysis of variance. For each device comparison (Roche IDS vs. MiniMed, Roche IDS vs. Animas, and MiniMed vs. Animas), the primary end point was then compared by means of a two-sample t test on a two-sided level of significance \( z = 0.05 \). In addition, two-sided 95% confidence intervals were presented.

For continuous variables, the descriptive statistics are presented. For categorical variables, frequencies and percentages were computed. Parametric 95% confidence intervals were determined. Simple comparisons between groups and subgroups are based on t tests or Wilcoxon tests and on logrank tests, if time-to-event data were analyzed. The distribution of the bG values was checked for normality by the Shapiro-Wilk test. Statistical analysis was performed using SAS version 9.1.3 service pack 4 (SAS Institute, Cary, NC).

**Results**

All 24 enrolled subjects completed the study. Many subjects required significant adjustments in their basal rate and insulin therapy parameters prior to initiation of the in-clinic study phase. No severe AEs were reported. The primary end point bG was calculated based on 23 subjects; data from one subject
Table 2. Primary End Point: Mean Differences by Subject of 6-h BG Values to 110 mg/dL (n = 23)

<table>
<thead>
<tr>
<th>Device</th>
<th>Value (mg/dL)</th>
</tr>
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<tbody>
<tr>
<td>Roche IDS</td>
<td>18.8 ± 33.8</td>
</tr>
<tr>
<td>Animas</td>
<td>17.3 ± 30.9</td>
</tr>
<tr>
<td>MiniMed</td>
<td>47.4 ± 31.8</td>
</tr>
</tbody>
</table>

Data are mean ± SD values. Statistically significant differences were seen between the Roche Insulin Delivery System (IDS) and the MiniMed devices ($P = 0.0049$) and between the Animas and MiniMed devices ($P = 0.0022$).

were excluded because of a protocol violation (inadvertent insulin pump disconnection).

The mean difference between 6-h BG levels following test meals and the 110 mg/dL BG target for the MiniMed device was significantly higher than for the Roche IDS ($P = 0.0049$) and Animas ($P = 0.0022$) devices (Table 2). The resulting mean BG levels at 6 h were 157.4 ± 31.8 mg/dL for the Medtronic device, 128.8 ± 33.8 mg/dL for the Roche IDS device, and 127.3 ± 30.9 mg/dL for the Animas device. When calculated for test meals with 2-h BG >140 mg/dL that received a bolus recommendation, significant similar differences in 6-h BG compared to target values were also seen (Table 3).

As presented in Figure 3, the reduced insulin bolus in test meals resulted in 2-h postprandial hyperglycemia (>140 mg/dL) for a similar number of meals with all three ABCs. The Roche IDS and Animas devices recommended 2-h correction boluses significantly ($P = 0.0001$ for Roche IDS, $P = 0.0002$ for Animas) more frequently than the MiniMed device even though the 2-h postprandial BG levels were lower with the Roche IDS and Animas devices (231.6 ± 37.8 mg/dL and 226.4 ± 38.2 mg/dL, respectively) than with the MiniMed device (260.3 ± 32.3 mg/dL). Significantly more of the meals managed by the Roche IDS and Animas returned to target range after the correction boluses than those managed by the MiniMed device ($P = 0.0002$ for Roche IDS, $P = 0.0040$ for Animas); the difference between the Roche IDS and Animas devices was not statistically significant.

At 2 h following all test meals, the Roche IDS device recognized significantly ($P < 0.0001$) less remaining active insulin (0.35 ± 0.49 units) compared to the MiniMed device (2.14 ± 0.93 units) and the Animas device (1.76 ± 0.77 units) for all meals with 2-h BG >140 mg/dL, prompting a larger correction bolus dose (1.45 ± 0.92 units) compared to the Animas device (1.26 ± 0.96 units) and MiniMed device (1.04 ± 0.77 units).

During the 44-h time interval with each ABC (the first hours until 04:00 h were excluded because of carryover from the previous ABC), subjects using the Roche IDS and Animas devices remained within the BG target range significantly ($P = 0.0301$ for Roche IDS and $P = 0.0563$ for Animas) longer (19.8 and 19.9 h, respectively) than when using the MiniMed device (15.2 h). Mean BG at the 44-h interval for the MiniMed device (162.3 ± 49.6 mg/dL) was significantly ($P = 0.0432$ for Roche IDS and $P = 0.0210$ for Animas) higher than for the Roche IDS (147.0 ± 49.7 mg/dL) or Animas (144.4 ± 50.7 mg/dL) devices.

There were no severe hypoglycemic events during the course of the study. A total of 91 hypoglycemic events (as defined in Research Design and Methods) occurred during the in-clinic phase of the study. Of these events, 14 occurred following test meals; however, only four of these events occurred following test meals that received a correction bolus: two events occurred with the Roche IDS device and two with the Animas device. These were not severe hypoglycemic events, nor was the difference between groups statistically significant. The 77 remaining events occurred following compensation meals and/or overnight. There were no statistically significant differences in the number of hypoglycemic events between the ABCs. One hyperglycemic event occurred following a test meal.

Conclusions

Previous studies have looked at the clinical utility of ABCs in comparison to manual bolus calculation. This study is the first head-to-head clinical trial to compare the efficacy of three ABCs in managing postprandial glycemia in a controlled clinical setting. Results from this study showed that use of ABCs can assist in achieving postprandial glucose control without significant hypoglycemia; however, there were significant differences among the ABCs evaluated. Specifically, we found that the Roche IDS and Animas devices recommended correction insulin boluses and achieved target BG levels following correction bolus administration more frequently compared with the MiniMed device. There are differences in the ways each device determines remaining active insulin (which will impact the correction dose calculation); however, these differences can only explain in part why both the Roche IDS and Animas systems performed significantly better than the MiniMed device.

Although the manufacturers of all three ABCs recommend setting a BG target range, we believe that a potential limitation in the performance of the MiniMed device was the manner in which the BG target value is determined. In contrast to the Roche IDS and Animas devices, which correct to the midpoint of the preprogrammed BG target range, the MiniMed device corrects only to the limits of the target range. This not only

Table 3. Mean Premeal and 2-h and 6-h Postprandial Blood Glucose for Test Meals with 2-h Blood Glucose >140 mg/dL That Received a Bolus Recommendation

<table>
<thead>
<tr>
<th>Device</th>
<th>Number of meals</th>
<th>Preprandial (mg/dL)</th>
<th>2-h postprandial (mg/dL)</th>
<th>6-h postprandial (mg/dL)</th>
<th>Bolus recommendation at 2 h (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche IDS</td>
<td>45</td>
<td>110.8 ± 31.4</td>
<td>231.6 ± 37.8</td>
<td>120.8 ± 34.7</td>
<td>1.45 ± 0.92</td>
</tr>
<tr>
<td>Animas</td>
<td>45</td>
<td>108.3 ± 31.2</td>
<td>226.4 ± 38.2</td>
<td>126.7 ± 42.4</td>
<td>1.26 ± 0.96</td>
</tr>
<tr>
<td>MiniMed</td>
<td>22</td>
<td>127.0 ± 39.1</td>
<td>260.3 ± 32.3</td>
<td>154.6 ± 37.0</td>
<td>1.04 ± 0.77</td>
</tr>
</tbody>
</table>

Data are mean ± SD values.
impacts the amount of correction insulin recommended but whether the device even recommends a correction. We believe that narrowing the target range for the MiniMed system (e.g., 109–111 mg/dL) may have yielded different results. MiniMed generally advises patients to use the preprandial and post-prandial bG target range (based on physician advice) when setting pump parameters.

An important finding was that most of the patients we enrolled had been using inappropriate basal rates and inaccurate insulin therapy parameter settings (ISF, I:CHO, acting time). It is important that clinicians who manage patients on insulin pump therapy periodically perform comprehensive assessments to check the accuracy of these parameters. Basal rates and insulin therapy parameters must be optimized for successful use of ABCs.

It is important to note that the necessity to use conservative Meal Rise and Offset Time settings on the Roche IDS device (to account for the diversity of the study group) may have somewhat limited the performance of the Roche IDS device in controlling postprandial hyperglycemia. In a real-world situation, settings for these features would likely be programmed to the individual needs of each patient. The impact of adjustment of these features was recently demonstrated in a small, in vitro study that looked at how the Roche IDS, MiniMed, and Animas devices managed postprandial hyperglycemia.21

In summary, all three of the ABCs studied demonstrated the ability to control postprandial hyperglycemia without significant hypoglycemia; however, the MiniMed device was significantly less effective than the Roche IDS and Animas devices. Furthermore, less than half of all test meals with >140 mg/dL at 2 h actually returned to target range at 6 h. This may be due to restrictions inherent to the study in using static bolus calculator parameters; in clinical settings, patients and clinicians would tailor these settings to the individual. Features that allow for more individualization of insulin therapy may differentiate the performance of the ABCs in actual patient use. Use of ABCs has been shown to improve glycemic control8–10; however, it is important that insulin therapy parameters are accurate and that patients and practitioners know how to use an ABC appropriately.

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References


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