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ORIGINAL ARTICLE

Benefits of Blinded Continuous Glucose Monitoring during a Randomized Clinical Trial

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Abstract

Background:

Real-time, personal continuous glucose monitoring (CGM) is a validated technology that can help patients improve glycemic control. Blinded CGM is a promising technology for obtaining retrospective data in clinical research where the quantity and quality of blood glucose information is important. This study was designed to investigate the use of novel procedures to enhance data capture from blinded CGM.

Methods:

Following a 4-week run-in, 46 patients with type 1 diabetes were randomized to one of two prandial insulins for a 12-week treatment period, after which they were crossed over to the alternate treatment for 12 weeks. Continuous glucose monitoring was implemented at the end of run-in (practice only) and during the last 2 weeks of each treatment period. Eighty percent of 288 possible daily glucose values were required for at least three days. Continuous glucose monitoring was extended for an additional week if these criteria were not met, and patients were allowed to insert sensors at home when necessary. Continuous glucose monitoring results were compared to reference eight-point self-monitoring of blood glucose (SMBG).

Results:

Higher than expected sensor failure rate was approximately 25%. During run-in, 12 of 45 attempted profiles failed adequacy criteria. However, treatment periods had only 1 of 82 attempted profiles considered inadequate (6 cases required an additional week of CGM). Using SMBG as reference, 93.7% of 777 CGM values were in Clarke error grid zones A+B.

Conclusions:

With appropriate training, adequate practice, and opportunity to repeat blinded CGM as needed, nearly 100% of attempted profiles can be obtained successfully.

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Abbreviations: (CGM) continuous glucose monitoring, (SD) standard deviation, (SMBG) self-monitoring of blood glucose

Keywords: clinical trial, continuous glucose monitoring, diabetes mellitus, self-monitoring of blood glucose

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Introduction

Continuous glucose monitoring (CGM) is an emerging technology with promise to substantially alter the treatment of diabetes.[1–5] The Juvenile Diabetes Research Foundation CGM trial results have demonstrated that both adult and pediatric patients with type 1 diabetes mellitus (T1DM) who are compliant with CGM can achieve clinically meaningful improvements in glycemic control.[6–8] Continuous glucose monitoring sensor-augmented insulin pump therapy has been demonstrated to result in significant improvements in glycated hemoglobin levels when compared to intensive multiple daily injection treatment of T1DM.[9]

In addition to the use of unblinded, real-time CGM to improve the treatment of diabetes, CGM can be employed in a blinded mode to augment traditional data sources in clinical trials designed to compare diabetes treatments.[10] Continuous glucose monitoring is an important adjunctive data collection tool that provides an enriched data set compared to the relatively sparse information available from intermittent self-monitoring of blood glucose (SMBG). "Best practices" or optimal protocols for the use of blinded CGM in this setting have not been fully explored, although retrospective CGM was successfully employed using early generation CGM devices to compare subcutaneous insulin infusion to conventional treatment[11,12] and in a pilot study comparison of insulin mixtures.[13] None of these studies, however, reported information regarding success rates for CGM data collection. The study by Weintrob and colleagues[11] did report on CGM data reliability by cross correlation of CGM to SMBG data.

By design, current blinded CGM technologies do not provide any direct, useful feedback to facilitate diabetes management. The added burden of daily CGM calibration procedures and sensor insertion may complicate a clinical trial subject's day-to-day life and can present a barrier to patient compliance with protocol procedures. Therefore, efforts to minimize patient hardship are well advised to avoid potential loss of data attributable to patient- or device-related issues. Investigators need to seek a balance, not overburdening patients, but building in "best practices" to maximize the quality and quantity of data obtained. This communication describes successful implementation of blinded CGM data collection during a randomized clinical trial.

Methods

Forty-eight generally healthy patients with at least 12 months of T1DM were enrolled in a study comparing two different prandial insulin products. Following a 4-week run-in period, during which patients received standard therapy while being trained in optimal diabetes self-care principles, patients were randomly assigned to receive one prandial insulin treatment for 12 weeks, after which they crossed over to the other treatment for an additional 12 weeks. Secondary endpoints of the study included a variety of CGM-derived indices (e.g., mean glucose; time spent between 71 and 140 mg/dl; area under the curve >140, >180, ≤70 mg/dl).

Study coordinators and investigators received training on deployment of the device used in this study (DexCom™ SEVEN PLUS®, DexCom, Inc., San Diego, CA) from the sponsor, the clinical research organization representing the sponsor, and the device manufacturer. Three weeks into the 4 week run-in period, patients were trained in sensor insertion and blinded CGM device use. The patients returned to the investigative site after 1 week for sensor removal and data upload. During this week, the patients also used the OneTouch™ Ultra™2 (LifeScan, Inc., Milpitas, CA) blood glucose meter to record eight-point SMBG tests (before and 2 h after meals, at bedtime, and at 3:00 AM), which were used as baseline for the study's primary endpoint analysis. The CGM system records mean glucose values every 5 min (288 records/day); systems such as the one employed in this trial are subject to periodic data gaps whenever the data-recording receiver is located more than 5 ft. from the data transmitter that is located at the sensor insertion site. Thus CGM data were assessed for adequacy based on the following criterion: data points needed to be present for at least 80% of the possible 288 glucose values per day for at least 3 days, starting on the day after sensor insertion. Data collected during the first day of sensor use was discarded since it may be somewhat less reliable than data collected toward the middle of a 7 day session,[5] and thus the primary, predefined CGM data analysis was based on days 2–4 of sensor wear. If a patient's CGM data failed the adequacy criterion during the run-in period, the CGM session was not repeated.

Continuous glucose monitoring data from the run-in period were not used for clinical trial analyses; these

CGM sessions served only as practice for the patients and the investigators for subsequent collections during the treatment periods. Continuous glucose monitoring was initiated again 2 weeks before the end of each 12-week treatment period. As in the run-in period, eight-point SMBG profiles were also collected on 3 days during these last 2 weeks of each treatment period. Patients were dispensed an extra glucose sensor for insertion at home if a sensor failure signal was indicated by the CGM device during the data collection week. When they returned to the clinic, the CGM data were uploaded and immediately analyzed. If the adequacy criterion was not met, then subjects were instructed to perform another week of blinded CGM prior to the crossover visit. The same procedures were followed at the end of the second treatment period.

The study design allowed for the retrospective evaluation of CGM and SMBG data, using the SMBG as a reference value for the CGM data. The pairing was performed by correlating the CGM value obtained immediately prior to the SMBG value. This procedure does not account for the lag time of 5–10 minutes that this system is known to experience when comparing CGM values to reference YSI (YSI Life Sciences, Yellow Springs, OH) blood glucose values.[5,14] Continuous glucose monitoring system calibration was performed in accordance with the manufacturer's users guide instructions, with a minimum calibration frequency of every 12 hours. The data sets were correlated using CGM values obtained *prior* to the corresponding SMBG values as a general practice to minimize any potential bias in data following a calibration entry. Coupled with the fact that lag time was ignored, this correlation represents a "worst case" scenario for the CGM system.

The matched CGM–SMBG data were used to quantify CGM performance in reference to SMBG. Analysis based on the Bland–Altman plot is presented to test for agreement between the two measurement methods. Linear regression was also used to evaluate the relationship between the matched data sets. Clarke error grid analysis[15] was used to quantify the clinical accuracy of CGM in reference to SMBG data.

Results

During this trial, the sensor failures (defined as sensors that did not provide at least four days of CGM data to allow analysis of data from days 2–4) were approximately 25%; this unexpectedly high sensor failure rate was due to a manufacturing issue (since resolved) that occurred during the time that this trial was underway (personal communication from DexCom). At the end of the run-in period, 12 of 45 attempted profiles failed to meet the predefined adequacy criteria, a rate that is consistent with the overall sensor failure rate observed during the trial. However, at the end of the first treatment period, none of 42 attempted profiles failed adequacy criteria; 39 successful glucose profiles were obtained during the first week, and 3 patients required a second week of blinded CGM to achieve success. At the end of the second treatment period, only 1 of 40 attempted profiles failed adequacy criteria; 36 were successful during the first week, 3 required the second week, and 1 patient failed during the first week and declined to attempt a second week. Of the 82 successful profiles obtained during the treatment periods, the mean percentage of total possible CGM data points collected over the entire data acquisition period (at least 3 and up to 6 days) was 95 ± 3.4 [standard deviation (SD)] percent, with a range of 86–100 percent. Overall CGM data collection success rate according to protocol-defined criteria was 99%.

A substantial data set to cross correlate CGM and SMBG, with 777 paired points, was available for evaluating CGM performance retrospectively in reference to SMBG. The Bland–Altman plot, **Figure 1**, indicates comparable random differences as a function of mean concentration, with a bias of 2.7 mg/dl and limits of agreement (95%) of ±74 mg/dl. Linear regression analysis showed the slope of the linear curve fit to be 0.998 (95% confidence interval 0.98–1.01), and CGM data were significantly correlated to SMBG measurements. The following traditional

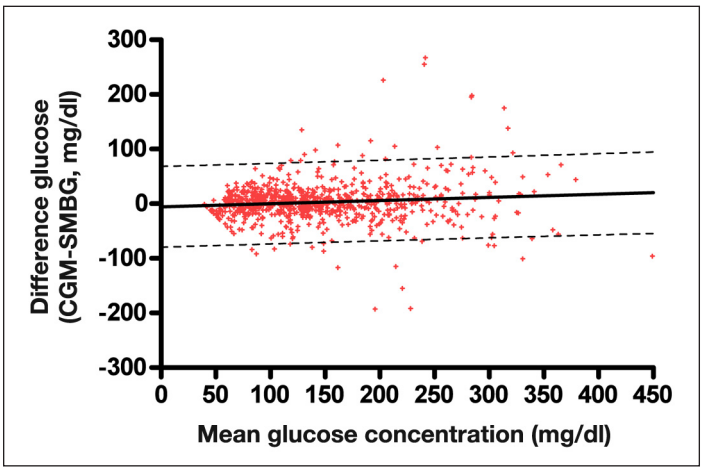

Figure 1. Bland–Altman plot of the difference in glucose concentration as a function of mean glucose concentration for CGM sensor and SMBG data. The least squares best fit line with 95% prediction bands are displayed.

measures of sensor accuracy are provided, but they must be interpreted cautiously, as the reference SMBG measurements are less accurate than traditional reference methods. The mean absolute error was 24 mg/dl (SD ± 29) with a mean absolute relative error of 19% (SD ± 24). Fifty-seven percent of values <75 mg/dl by SMBG were within 15 mg/dl (inclusive) by CGM, and 74% of values ≥75 mg/dl by SMBG were within 20% (inclusive) by CGM. Clarke error grid analysis (**Figure 2**) showed 93.7% of values resided within clinically acceptable zones A and B (71.8% in zone A, 21.5% in zone B), 0.9% in zone C, 5.3% in zone D, and a single reading (0.1%) was in zone E.

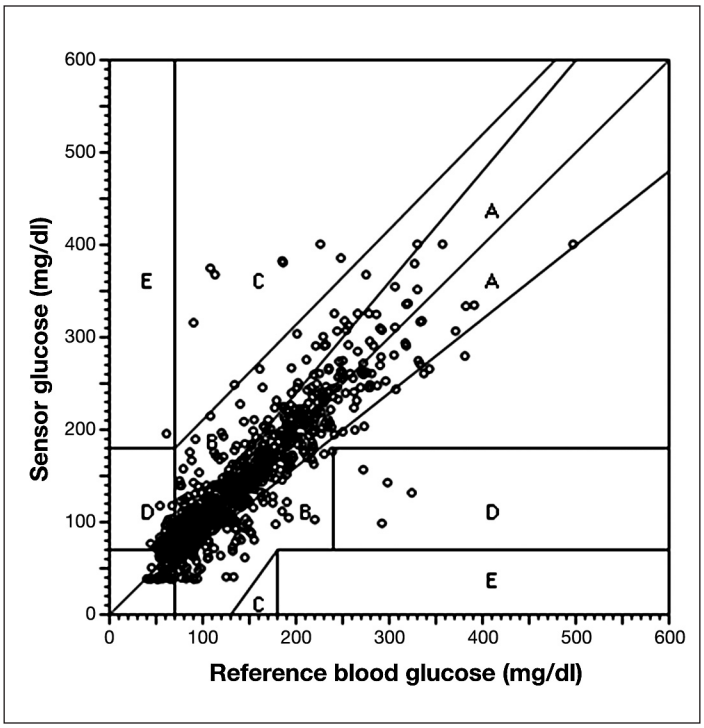

Figure 2. Clarke error grid analysis of CGM sensor data using SMBG data as the reference standard.

Discussion

Blinded CGM has been employed in a variety of settings, including comparison of diabetes treatments,[11–13] detecting and preventing hypoglycemia,[16,17] and diagnosing and monitoring insulinoma.[18] The present study describes the successful implementation of blinded CGM with best practices to ensure acquisition of a robust data set in a clinical trial designed to compare diabetes treatments. Blinded CGM is a valuable tool to collect detailed glycemic excursion data in either the ambulatory or hospital setting while diminishing the possibility that the data-collection process itself may alter the outcomes being tested. This is particularly relevant in open-label treatment trials where knowledge of both the treatment and the measured outcome could lead to bias in the results. Even when the treatments being tested are blinded, the use of unblinded CGM may alter patient behavior and potentially limit the broad applicability of study results to SMBG-only settings.

Successful implementation of blinded CGM poses special challenges across several fronts. Successful CGM requires patient and provider education and support. Because patients do not have access to the real-time glucose results during blinded CGM, the data-collection process may be perceived as a nuisance or, worse, an unacceptable burden. This makes it essential to use blinded CGM in a user-friendly fashion defined by comfort, long sensor life, minimal calibration restrictions, freedom from bulky hardware, and avoiding excessively long periods of sensor use as a primary strategy to ensure adequate data collection. As this technology matures further, these potential tradeoffs should recede in importance, but currently, these considerations may help drive decisions regarding choice of hardware systems to employ in a particular clinical study.

Another challenge derives from the assessment of whether blinded CGM data collection has been successful in real time versus after the CGM process has been completed; this can lead to missing data that cannot be recovered after the fact. The higher-than-expected sensor failure rate observed in the present study could have confounded this problem further, but the CGM technology selected had real-time alerts for early sensor failures during blinded CGM use, which enabled subjects to replace these sensors at home and thus avoid potential large gaps of missing data. Perhaps this multiplicity of issues explains the paucity of clinical trial reports that have employed blinded CGM endpoints to compare diabetes treatments despite the fact that blinded CGM can offer substantial insights into these comparisons. In any case, these issues prompted us to develop a program of use for blinded CGM in a clinical trial that would not overburden patients and yet provide a solid and complete data set for analysis that could succeed even in the face of unforeseen circumstances (such as the excessive sensor failure rate that occurred during this trial). The adequacy of sampling achieved (>80% of possible readings during days 2–4 of CGM obtained in 99% of attempted profiles) along with the agreement between CGM values and the reference SMBG values (**Figures 1** and **2**) demonstrate that the protocol described here achieved its goals.

Conclusions

By combining investigator, coordinator, and patient training with early practice to establish familiarity with a blinded CGM system, and with the implementation of failsafe procedures (e.g., allowing subjects to replace/insert sensors from home as necessary, assessing adequacy of data collection and allowing for a repeat collection period as needed, and predefining the threshold for an "adequate" amount of data acquisition for a CGM session) designed to protect against missing data, we have developed a CGM implementation protocol that is able to overcome both expected and unexpected data-collection hurdles. This set of procedural safeguards may provide a template for broader successful use of blinded CGM in diabetes treatment comparison trials.

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Disclosure:

All authors are employees of Halozyme Therapeutics, Inc., the sponsor of this study.

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