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Accuracy of the GlucoWatch G2 Biographer and the Continuous Glucose Monitoring System During Hypoglycemia. Experience of the Diabetes Research in Children Network (DirecNet)

The Diabetes Research in Children Network (DirecNet) Study Group*

Abstract

Objective—To assess the accuracy of the GlucoWatch® G2™ Biographer (GW2B) and the Continuous Glucose Monitoring System (CGMS™) during hypoglycemia in children and adolescents with type 1 diabetes mellitus (T1DM).

Research Design and Methods—During a 24-hour clinical research center stay, 91 children and adolescents with T1DM (aged 3.5 to 17.7 years) wore 1 or 2 CGMSs and 89 of these subjects wore 1 or 2 GW2Bs. Frequent serum glucose determinations were made during the day, overnight and during insulin-induced hypoglycemia resulting in 192 GW2B-reference pairs and 401 CGMS-reference pairs during hypoglycemia (reference glucose ≤60 mg/dL).

Results—During hypoglycemia, the median absolute difference between the 192 GW2B-reference glucose pairs was 26 mg/dL and between the 401 CGMS-reference glucose pairs was 19 mg/dL, with 31% and 42% respectively of the sensor values within 15 mg/dL of the reference glucose. Sensitivity to detect hypoglycemia when the GW2B alarm level was set to 60 mg/dL was 23% with a false alarm rate of 51%. Analyses suggested that modified CGMS sensors that became available in November 2002 may be more accurate than the original CGMS sensors (median absolute difference 15 vs. 20 mg/dL).

Conclusions—These data show that the GW2B and the CGMS do not reliably detect hypoglycemia. Both of these devices perform better at higher glucose levels suggesting they may be more useful in reducing HbA1c levels than in detecting hypoglycemia.

Hypoglycemia remains a major obstacle to successful treatment of type 1 diabetes mellitus (T1DM), especially in children. In adolescents with T1DM, the risk of severe hypoglycemia is greatly increased compared with adults, regardless of the intensity of treatment.(1) In young children with T1DM, there are heightened concerns that hypoglycemia will cause permanent neurologic sequelae.(2,3) Across all age groups, the possibility of a severe hypoglycemic event occurring at school, at play, or at night is one of the greatest fears of patients and parents alike. (4)

The introduction of near-continuous glucose monitors represents a technologic advance that may be particularly useful in the management of youth with T1DM. Two such devices are currently FDA approved: the GlucoWatch® G2™ Biographer (“GW2B”; developed and manufactured by Cygnus, Inc., Redwood City, CA; marketed and distributed by Sankyo

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Pharma Inc.), which provides real-time measurements of interstitial glucose concentrations at 10 minute intervals, and the Continuous Glucose Monitoring System, CGMS™ ("CGMS"; Medtronic MiniMed, Northridge, CA), which stores glucose values obtained every 5 minutes for a retrospective review. The GW2B is equipped with an alarm to signal hypoglycemia and pending hypoglycemia as well as hyperglycemia. The accuracy of the GW2B has been reported in several studies(5–10) but data in children are limited(11) and prior studies have not systematically evaluated sensor function during acute hypoglycemia. There have been several reports of frequent and prolonged hypoglycemia during the night when using the CGMS. (12–15) However, recent studies have raised questions regarding the accuracy and reproducibility of the CGMS.(15–17)

The purpose of this paper is to report the accuracy of the CGMS and GW2B during hypoglycemia occurring either spontaneously or during an insulin-induced hypoglycemia test in children with T1DM.

Methods

The study was conducted by the Diabetes Research in Children Network (DirecNet). The study protocol, statistical methods, and informed consent procedures have been described in prior publications(18,19) and are briefly summarized herein.

The major eligibility criteria for the subjects included age 1 to <18 years, a clinical diagnosis of type 1 diabetes and insulin therapy (either a pump or injections) for at least one year. Each subject used the GW2B and CGMS during a 24-hour Clinical Research Center (CRC) admission. To assess CGMS function over the entire 72 hours of its lifespan, one-third of the subjects had the CGMS inserted 48 hours prior to admission, one-third 24 hours prior to admission, and one-third on admission to the CRC. Subjects were offered the option of wearing a second CGMS during the inpatient stay. Following admission to the CRC, a GW2B sensor was placed and calibrated. A second GW2B sensor was placed at a later time so that there would be a minimum two hour overlap between the two GW2Bs and such that at least one GW2B would be functioning for the 24 hours of serum glucose measurements. A One Touch® Ultra® Meter ("Ultra"; Lifescan, Milpitas, CA) was used to obtain glucose measurements for calibrating the sensors.

Blood samples were obtained hourly during the day, every 30 minutes overnight, every 5 minutes for up to 90 minutes during an insulin-induced hypoglycemia test, and at additional times when the sensors were calibrated or if there were symptoms of hypoglycemia. Glucose measurements were made at the DirecNet Central Biochemistry Laboratory at the University of Minnesota using a hexokinase enzymatic method.

Subjects ≥7 years of age and of sufficient weight to accommodate extra blood sampling underwent an insulin-induced hypoglycemia test. The purpose of the hypoglycemia test was to assess sensor function during an acute fall in glucose levels into the mildly hypoglycemic range. If the pre-test blood glucose was <80 mg/dL, juice or other carbohydrate was given orally to raise the blood glucose above this level before starting the test. For the test, 0.05–0.10 units per kg body weight of regular insulin was given by intravenous bolus injection. After 30 minutes, a second dose could be given if the target glucose (<55 mg/dL) had not been achieved. For subjects who did not reach a glucose level below 55 mg/dL, the test ended after 90 minutes. For the subjects whose glucose decreased below 55 mg/dL, sampling continued every 5 minutes following hypoglycemia treatment until the glucose level was above 80 mg/dL. Treatment of hypoglycemia was with either oral or intravenous glucose at the discretion of the investigator.

For analysis, the GW2B glucose values were adjusted for a 17.5 minute lag time and matched to reference serum glucose measurements drawn within ± 5 minutes of the sensor reading

except during the insulin-induced hypoglycemia test where the matching was within ± 2.5 minutes. The CGMS glucose values were matched to reference serum glucose measurements drawn within 2.5 minutes of the sensor reading after adjusting for a CGMS lag time of 2.5 minutes. The lag times for the GW2B and CGMS principally represent the time involved to sample the interstitial fluid and measure the glucose. Thus, the GW2B value, when it appears on the device, represents the glucose level 15–20 minutes earlier.

The absolute difference was defined as the absolute value of sensor glucose value minus the reference glucose value. Sensitivity was defined as the percentage of reference values ≤60 mg/dL in which the sensor was also ≤60 mg/dL. The false alarm rate was calculated as the percentage of sensor values ≤60 mg/dL in which the reference value was >60 mg/dL. During the course of the study, Medtronic MiniMed modified the sensor fabrication process that had been used since 1999. Accuracy analyses were conducted separately for the “original” and “modified” sensors. Statistical comparisons of the original versus modified CGMS sensors were conducted using the bootstrap (a re-sampling technique to determine the statistical margin of error).(20)

Hypoglycemic episodes occurring overnight (11pm–6am) were defined as periods with at least two sensor glucose readings ≤60 mg/dL and no readings >70 mg/dL (the episode was considered to have ended when the glucose reading was >70 mg/dL). Episodes were required to be separated by a period of at least 30 minutes with all sensor readings >70 mg/dL. Only episodes during which there was at least one reference glucose measurement were counted. The episode was considered to be confirmed if there was at least one reference glucose value during the period that was ≤70 mg/dL and not confirmed if all reference values were >70 mg/dL.

Results

The study included 91 subjects ranging in age from 3.5 to 17.7 (mean 9.9) years; 51% were female and 85% were Caucasian.

GW2B

The reference glucose was ≤60 mg/dL for 192 of the 3,672 GW2B-reference glucose paired values. For the 192 reference glucose values ≤60 mg/dL, the median absolute difference of the GW2B values was 26 mg/dL; 31% of sensor values were within 15 mg/dL of the reference value.

Results were similar for hypoglycemic reference values compared with GW2B values obtained during the IV insulin test and those obtained at other times (Table 1). Among 45 subjects undergoing the IV insulin test, the reference glucose nadir was ≤60 mg/dL in 34 subjects wearing 48 GW2Bs during the test. Of these, the GW2B nadir was also ≤60 mg/dL for 12 (25%) cases, 61–80 mg/dL for 27 (56%), 81–100 mg/dL for 8 (17%), and >100 mg/dL for 1 (2%). Among the 11 subjects wearing 16 GW2Bs in whom the reference glucose nadir was >60 mg/dL, the GW2B nadir was ≤60 mg/dL in 1 of the 16 (6%).

For a hypoglycemia alarm setting of 60 mg/dL, GW2B sensitivity for detection of an actual serum glucose level ≤60 mg/dL (based on the reference glucose value) would be 23%; 51% of alarms would be false. The reference glucose was >80 mg/dL for 18% of these GW2B alarms ≤60 mg/dL. As can be seen in Table 2, greater sensitivity for detecting a true glucose value ≤60 mg/dL would be achieved by raising the alarm setting, but this is at the expense of progressively higher false alarm rates.

During overnight monitoring (11:00 PM to 6:00 AM), the GW2B reported 21 hypoglycemic episodes occurring in 16 subjects. A reference glucose value was obtained during 18 of the episodes. Hypoglycemia (reference value ≤60 mg/dL) was confirmed in 10 (56%) of the 18 episodes. In the 8 non-confirmed episodes, the lowest reference glucose value ranged between 75–108 mg/dL.

CGMS

The reference glucose was ≤60 mg/dL for 401 of the 6,778 CGMS-reference glucose paired values. For the 401 reference glucose values ≤60 mg/dL, the median absolute difference of the CGMS values was 19 mg/dL; 42% of sensor values were within 15 mg/dL of the reference value. There were 356 CGMS-reference glucose pairs from original CGMS sensors and 45 pairs from modified sensors. The median absolute difference was 20 mg/dL for the original sensors compared with 15 mg/dL for the original sensors (p=0.09).

Results for hypoglycemia occurring during the IV test and at other times are presented in Table 1 for the original and modified sensors. During the IV insulin test, the reference glucose nadir was ≤60 mg/dL in subjects using 51 original sensors and 3 modified sensors. For the 51 original sensors, the sensor nadir was ≤60 mg/dL in 26 (51%), 61–80 mg/dL in 11 (22%), 81–100 mg/dL in 12 (24%), and >100 mg/dL in 2 (4%). For the 3 modified sensors, the sensor nadirs were 42, 48, and 77 mg/dL. Among the 10 subjects wearing 14 original CGMSs in whom the reference glucose nadir was >60 mg/dL, the CGMS nadir was ≤60 mg/dL in 2 of the 14 (14%). Among the 6 modified CGMSs worn by 3 subjects in whom the reference glucose nadir was >60 mg/dL, the CGMS nadir was also >60 mg/dL in all 6.

Since the CGMS is retrospectively calibrated, real-time sensitivity for detection of hypoglycemia cannot be assessed. However, we evaluated the data as if the same level of accuracy would be present with prospective calibration. For an alarm setting of 60 mg/dL, the sensor sensitivity for detection of a glucose level ≤60 mg/dL (based on the reference glucose value) would be 36% for the original sensors and 49% for the modified sensors (p=0.37), and 63% and 58% respectively of alarms would be false. The reference glucose was above 80 mg/dL for 39% and 15% of these original and modified CGMS alarms ≤60 mg/dL, respectively. As with the GW2B, greater sensitivity for detecting a true glucose value ≤60 mg/dL is achieved by raising the alarm setting, but this is at the expense of a higher false alarm rate (Table 2).

During overnight monitoring (11:00 PM to 6:00 AM), the CGMS reported 30 hypoglycemic episodes (as defined in the methods) occurring in 25 subjects with original sensors and 4 episodes in 4 subjects with modified sensors. For 26 of the episodes with the original sensors and for 3 of the episodes with a modified sensor, a reference glucose value was obtained during the episode. Hypoglycemia (reference value ≤60 mg/dL) was confirmed in 8 (31%) of the 26 events detected by the original sensors and in all 3 detected with the modified sensors. For 12 of the 18 unconfirmed episodes with the original sensors, the lowest reference glucose value was >100 mg/dL.

Discussion

This study was designed to evaluate the accuracy of the GW2B and CGMS in children and adolescents with T1DM. Since a critically important function of these sensors is in the detection and prevention of hypoglycemia, the current report focuses on performance of the devices during both induced and spontaneous reductions in serum glucose concentrations. Our results demonstrate that neither the GW2B nor the CGMS is accurate with respect to reporting glucose values in the hypoglycemic range. For reference serum glucose values that were ≤60 mg/dL, the median absolute differences of the GW2B and the original and modified CGMS sensors were 26, 20, and 15 mg/dL respectively and only 31%, 41%, and 51% of the sensor values

respectively were within 15 mg/dL of the reference glucose values. Additionally, reference glucose levels did not confirm a substantial fraction of the low sensor values reported by both systems. As we have reported in detail elsewhere,(18–19) the accuracy of the GW2B and the CGMS is considerably better when reference glucose levels are greater than 100 mg/dL.

A major benefit of real time compared with retrospective glucose sensing is the capacity to equip the system with hypoglycemia alarms. Consequently, we also explored the sensitivity and specificity of a range of alarm settings for the detection of hypoglycemia using the GW2B and reference serum glucose values. However, it must be remembered that the glucose value appearing on the device is estimating the serum glucose level 15–20 minutes earlier. As indicated in Table 2, the GW2B alarm would have to be set at 120 mg/dL in order to capture at least 90% of actual serum glucose concentrations that were ≤60 mg/dL. However, at this setting 85% of alarms would be false positives. Setting the alarm to trigger at a sensor value of 60 mg/dL would reduce the false alarm rate to 51%, but only 23% of true low reference glucose levels would be identified. For hypoglycemic episodes detected by the GW2B overnight, only 10 of 18 were confirmed by a reference serum glucose obtained during the episode. A previous GW2B accuracy study in 66 children reported that with an alarm setting of 90 mg/dL, sensitivity was about 90% to detect a reference glucose level ≤70 mg/dL but the false alarm rate was about 70%.(11) In our data, an alarm level of 90 mg/dL would detect 72% of values ≤70 mg/dL with a false alarm rate of 58%. In addition to its hypoglycemia alarm function, the GW2B has a “down-alert” function that alarms when the trend of sensor values indicates impending hypoglycemia. We are in the process of developing an analytic approach to assess this function of the GW2B.

The CGMS does not provide data in real time: glucose values are calculated using calibration values from both before and after the glucose sampling. Nevertheless, we evaluated how well the CGMS would alarm for hypoglycemia under the assumption that the accuracy would be similar in real-time. It is likely that accuracy would be lower with prospective calibration so these results should be considered to be the best case scenario for the CGMS. Similar to our findings with the GW2B, sensitivity was relatively low with an alarm setting of 60 mg/dL, though better with the modified sensors than with the original sensors. As with the GW2B, setting a higher alarm setting increased sensitivity but at the expense of a high false alarm rate.

For hypoglycemic episodes detected overnight by the original CGMS sensors, only 8 of 26 were confirmed by a reference serum glucose obtained during the episode. Although there were only three nocturnal episodes of hypoglycemia with the new sensors, all were confirmed by the reference glucose measurements. Several studies that have used the original CGMS sensors to evaluate metabolic control in children and adolescents with T1DM have reported an unexpectedly high incidence of asymptomatic hypoglycemia, especially at night.(12–14) McGowan and colleagues recently examined CGMS function at night in 7 children with T1DM. In that study, 4 of 5 nocturnal hypoglycemic episodes that were detected by the CGMS could not be verified by reference glucose measurements.(15) Guerci reported the CGMS’s sensitivity to detect hypoglycemia to be 33% (similar to what we found using original sensors). (21) Our data support the contention that previous clinical studies using the CGMS in children with T1DM overestimated the true incidence of hypoglycemia.

Since the GW2B and CGMS are more accurate in sensing high versus low glucose values, (18,19) the systems are likely to be of value in adjusting bolus and basal insulin doses in individuals with elevated HbA1c levels. For the GW2B, the accuracy for low glucose values limits the feasibility of its alarm function. While some users will accept a high false alarm rate in order to detect a high proportion of low glucose values, many will not. Thus, for many users, the greatest value of the GW2B may be for detecting trends and not for serving as a sentinel for hypoglycemia. The accuracy of this early generation of glucose sensors is reminiscent of

the early generations of glucose meters, which were less accurate than those currently available. Therefore, an expectation exists that future generations of sensors will have improved accuracy resulting in greater utility for the detection of hypoglycemia.

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Appendix

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