Spurious Reporting of Nocturnal Hypoglycemia by CGMS in Patients With Tightly Controlled Type 1 Diabetes

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OBJECTIVE — The Medtronic MiniMed Continuous Glucose Monitoring System (CGMS) is designed to continuously monitor interstitial fluid glucose levels within a range of 40–400 mg/dl. It is considered an important tool for overnight glucose monitoring. The goal of this study was to determine the accuracy of this system in individuals with tightly controlled diabetes.

RESEARCH DESIGN AND METHODS — Seven adolescents and young adults with HbA_{1c} levels 6.6 ± 0.6% (range 5.7–7.1) were admitted to the Clinical Research Center. Simultaneous glucose measurements obtained by glucose analyzer, Accu-Check Advantage meter, and CGMS were compared. The analyzer levels were considered the standard.

RESULTS — The CGMS results were lower than analyzer readings in 74% of simultaneous pairs of tests performed during the 24-h period; the average correlation was 0.76. There was a trend for the poorest correlation to occur in patients with the narrowest range in daily glucose levels. When the lowest CGMS reading of the night was compared with the simultaneous analyzer reading, the CGMS level was lower in all cases by an average of 38 ± 15%. In six of seven patients, the discrepancy was believed to be clinically significant; in at least four patients, overnight glucose levels reported by CGMS were falsely low, in a range that might have resulted in inappropriate reduction of overnight insulin dose.

CONCLUSIONS — CGMS reports of asymptomatic nighttime hypoglycemia may be spurious and should be interpreted with caution in patients with tightly controlled diabetes.

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Intensive diabetes management has been demonstrated to significantly reduce the long-term microvascular complications of type 1 and type 2 diabetes (1,2). To accomplish this, subjects have traditionally monitored blood glucose levels at least four times daily. However, intermittent testing has significant limitations and cannot accurately portray the tremendous variability in glucose levels that may occur throughout the day. Perhaps the most troubling problem with intensive management using intermittent testing is the increased risk of hypoglycemic events; subjects in the intensive management group of the Diabetes Control and Complications Trial experienced severe hypoglycemia two to three times more often than subjects receiving conventional therapy (1).

Sensors that continuously monitor glucose have long been sought as a tool to achieve better overall diabetes control. The Continuous Glucose Monitoring System (CGMS) (Medtronic MiniMed, Northridge, CA) is the first such device to be approved by the U.S. Food and Drug Administration and made available for clinical use. It is a Holter-style sensor system designed to continuously monitor interstitial fluid glucose levels within a range of 40–400 mg/dl. The glucose sensor is a microelectrode that is inserted into the subcutaneous tissue. The sensor generates an electronic signal, the strength of which is proportional to the amount of glucose present in the surrounding interstitial fluid. The signal is sent to the monitor, a portable, pager-sized device that records sensor signals every 5 min and converts them into blood glucose readings, providing 288 readings per day for up to 3 days. This gives a more accurate picture of daily blood glucose excursions than can be determined by fingerstick methods, allowing identification of the glycemic effect of food, activity, and insulin. It has been promoted as an important tool for overnight glucose monitoring because there are several reports of unrecognized nighttime hypoglycemia detected by the CGMS (3–7). In these reports, the CGMS readings were assumed to be accurate, despite lack of patient symptoms or confirmatory meter readings.

Limited experience with the CGMS in healthy individuals without diabetes suggested that the readings were not reliable in normoglycemic individuals, either because glucose levels were not reportable or because they were clearly erroneous. Medtronic MiniMed technical services stated that significant variation in blood glucose is necessary for the calibration between interstitial and plasma glucose, and therefore, the device may not be accurate in individuals who do not have diabetes. This led us to question whether CGMS results might be inaccurate in individuals with tightly controlled diabetes, leading to compromised clinical decision-making and jeopardizing health outcomes.

The following study was undertaken to evaluate the accuracy of CGMS glucose measurements in patients with tightly controlled diabetes and to determine

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Abbreviations: CGMS, Continuous Glucose Monitoring System.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Glucose variability throughout the 24-h study period and overnight from 10 P.M. to 7 A.M. as measured by SD of analyzer glucose levels and the correlation with simultaneously obtained CGMS and meter glucose levels*

Patient	1	2	3	4	5	6	7	Average
SD 24 h (mg/dl)	28	35	56	57	58	58	60	51
SD overnight (mg/dl)	15	18	59	55	59	42	30	39
Correlation								
CGMS vs. analyzer	0.50	0.70	0.98	0.87	0.56	0.83	0.95	0.76
Meter vs. analyzer	0.99	0.86	0.99	0.99	0.99	0.98	0.97	0.97

whether overnight CGMS readings in these patients would lead to appropriate treatment decisions.

RESEARCH DESIGN AND METHODS

Subjects

Seven adolescents and young adults with tightly controlled type 1 diabetes participated in this study. An eighth participant, a young man with cystic fibrosis–related diabetes, completed the study, but his data are not included because the CGMS was unable to measure his glucose values, perhaps because of cystic fibrosis–related alterations in the interstitial fluid electrolyte composition. Approval for this study was obtained from the University of Minnesota Committee for the Use of Human Subjects in Research; informed consent was obtained from all subjects.

Procedure

Subjects were admitted to the University of Minnesota General Clinical Research Center at 10:00 A.M. An intravenous catheter was inserted in a distal arm vein for blood drawing, and a baseline HbA_{1c} level was obtained. The CGMS was inserted into the subcutaneous abdominal fat tissue and calibrated over a 60-min period, as per standard Medtronic MiniMed operating guidelines.

Starting at 12:00 P.M., blood was drawn through the intravenous catheter every hour until 12:00 A.M., every 2 h between 12:00 and 6:00 A.M., and then hourly until 12:00 P.M. It was spun for immediate determination of plasma glucose level by a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). These levels are referred to as "analyzer glucose levels" in the current report and are considered the standard against which the other methods were compared. Simultaneous capillary plasma glucose levels were measured using the Accu-Check Advantage meter (Roche Diagnostics, Indianapolis, IN). These are referred to as "meter glucose levels" in the current report. The glucose levels measured before meals, at bedtime, and at 2:00 A.M. were entered into the CGMS for calibration purposes, as per the manufacturer's recommendations.

Patients had unrestricted access to food throughout the day and were given meals at typical times. They adjusted their premeal insulin as per their usual home routine. During the day, they engaged in light activities such as playing board games, watching television, and walking. The period from 10:00 P.M. to 7 A.M. was considered "nighttime."

Data analysis

The data from each CGMS unit were downloaded via a serial interface to a personal computer. Glucose levels obtained at each hour on the hour (every 2 h, 12:00 P.M. to 6:00 A.M.) were used to compare the three methods, with analyzer glucose levels considered the standard. While the CGMS gives a continuous readout over time, only the levels obtained on the hour, at the same time as the analyzer and meter levels, were used for analysis. Data are presented as mean ± SD.

Statistical analysis

Each participant had 21 sets of simultaneous glucose measurements by the three methods. Within subject means, standard deviations, and correlations were computed for these measurements. The measurements were compared according to zones of plasma glucose levels believed to be clinically significant.

RESULTS

Subjects

Four of the seven subjects were men, and the average age was 18 ± 3 years. All had well-controlled diabetes, with an average HbA_{1c} level of 6.6 ± 0.6% (range 5.7–7.1). The average duration of diabetes was 5.7 ± 7.1 years, with a range of 3 months to 15 years. Four individuals were on insulin pump therapy, and the other three received multiple daily injections.

Glucose levels during the 24-h study period

For all subjects during the 24-h study period, the average analyzer glucose reading was 133 ± 51 mg/dl. The average lowest glucose reading was 74 mg/dl; the average highest reading was 246 mg/dl. One subject achieved remarkably tight glucose control during the study (range 72–157 mg/dl) and a standard deviation of 28 mg/dl.

A comparison of simultaneous analyzer and CGMS results for all readings for all subjects showed that the CGMS results were lower in 74% of paired measurements, with a correlation between two methods of 0.76. Meter readings were generally closer to analyzer readings; the average correlation was 0.97. There was a trend for the poorest correlation to occur in the patients with the narrowest range in daily glucose levels (Table 1).

Overnight glucose readings

The average of the overnight glucose levels was quite similar between the three methods: analyzer 142 ± 32 mg/dl, meter 132 ± 32 mg/dl, and CGMS 130 ± 36 mg/dl. However, five of the seven subjects had hypoglycemia (glucose ≤70 mg/dl) recorded by CGMS during the night that was only verified by analyzer readings in one case. When the lowest CGMS reading of the night was compared with analyzer and meter readings obtained at the same time, the CGMS level was lower than the corresponding analyzer level in all seven patients, by an average of 38 ± 15% (Table 2). Only the CGMS levels obtained at the designated study times were used for data analysis and reporting, but these numbers were consistent with the general

Table 2—*Comparison of the lowest and highest nighttime CGMS glucose levels to simultaneous analyzer glucose levels (mg/dl), and the percent difference between them*

Patient	Lowest CGMS	Matched analyzer	% Difference	Highest CGMS	Matched analyzer	% Difference
1	<40	125	>68	131	138	5
2	64	111	42	178	135	−32
3	86	109	21	236	253	7
4	45	76	41	185	193	4
5	114	169	33	337	280	−20
6	70	103	32	187	167	−12
7	47	65	28	195	160	−22
Average	67 ± 26	108 ± 34	38 ± 15	207 ± 65	189 ± 57	−10 ± 15

Analyzer glucose levels were considered the standard.

trend of the CGMS glucose levels measured at 5-min intervals during the half hour before and after the study data time point. Average nighttime CGMS and analyzer readings are shown in Fig. 1.

Because CGMS data are intended for clinical use to guide treatment decisions, glucose levels were divided into "zones" believed to reflect levels that would prompt therapeutic intervention or dosage adjustment. Overnight glucose levels (seven values, 10:00 P.M. to 7:00 A.M.) were placed in the following zones: <60 mg/dl, urgent; 60–79 mg/dl, high-risk; 80–99 mg/dl, marginally low; 100–180 mg/dl, overnight desired range; and >180 mg/dl, high.

Only one patient had a lowest overnight CGMS reading in the correct clinical zone as measured by the corresponding analyzer glucose value (Figure 2). Six of the seven patients had CGMS readings that were in a lower zone than the actual zone indicated by the analyzer. In contrast, in five of seven patients, meter readings obtained at the same time point were in accordance with analyzer readings, whereas one was in a lower zone and one was in a higher zone.

The CGMS fared better with regard to correctly reporting high glucose readings. The highest overnight CGMS was somewhat lower than the analyzer readings in three cases and higher in four but overall differed by only 10 ± 15% (Table 2).

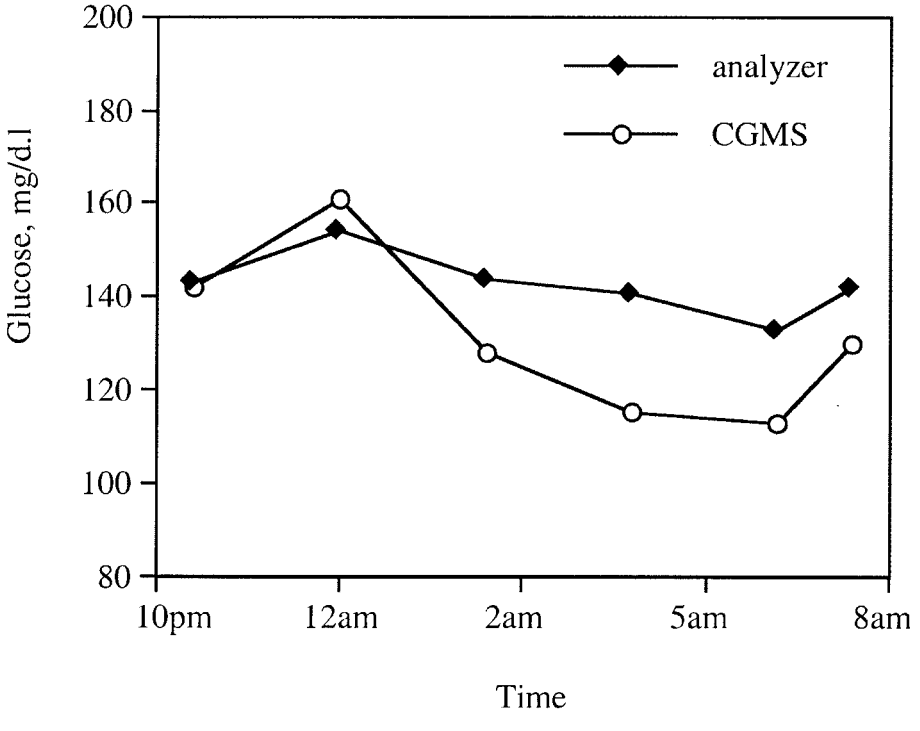

Figure 1—*Average overnight glucose readings by simultaneous CGMS and glucose analyzer measurement. Values were measured at 10:00 P.M., 12:00 A.M., 2:00 A.M., 4:00 A.M., 6:00 A.M., and 7:00 A.M.*

CONCLUSIONS — In the current study, the CGMS reported falsely low glucose levels overnight in six of seven persons with tightly controlled diabetes. At least four of these were in a range that might have resulted in inappropriate reduction in overnight insulin dosage. This has major clinical implications because the CGMS has become an increasingly common method for evaluation of overnight insulin requirements. Indeed, the CGMS has been touted as an important tool for discovering unsuspected nighttime hypoglycemia (3–6,8).

Although the CGMS has proved to be useful for improving HbA_{1c} levels in persons with poorly controlled type 1 diabetes (3,9,10), a high degree of unexpected asymptomatic nighttime hypoglycemia has been reported in these studies (3–6,8). The CGMS data were assumed to be accurate, although there were no simultaneous meter values for verification. One group reported that 70% of 56 children who wore the CGMS for 3 days had prolonged, frequent asymptomatic hypoglycemia (4). Others found that morning ketones were only positive in 1 of 11 reported occurrences of prolonged (greater than 30 min) overnight hypoglycemia (7), suggesting the hypoglycemia might not have been real. The present study was designed to specifically test the accuracy of the CGMS in subjects who had achieved tight control of diabetes (HbA_{1c} ≤7.1). In this population with relatively low standard deviation in glucose values, the CGMS clearly reported spuriously low glucose values.

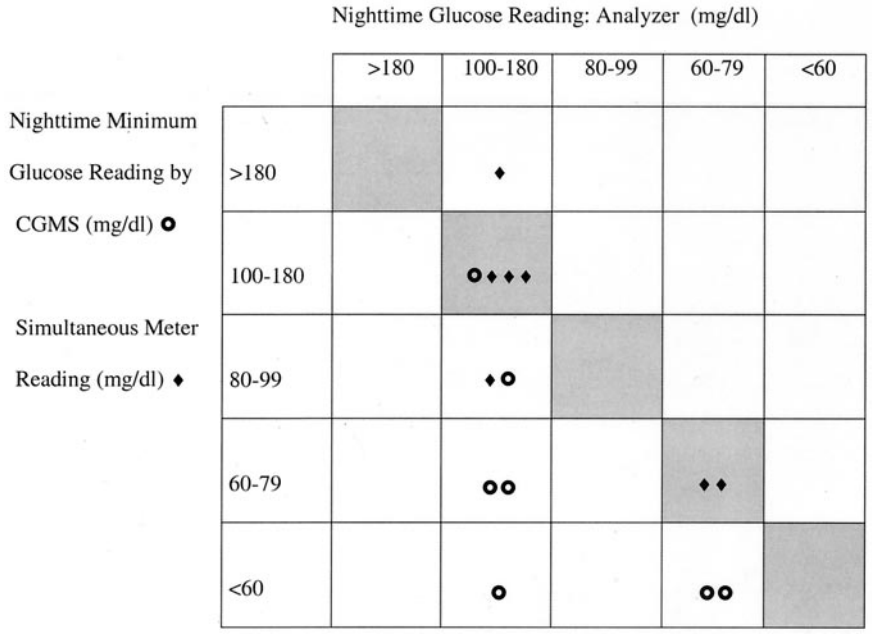

Figure 2—*Overnight glucose levels were measured between 10:00 P.M. and 7:00 A.M. in seven subjects. Each subject's lowest overnight CGMS glucose level (circles) and the simultaneously obtained meter glucose level (diamonds) were compared with the actual plasma glucose level measured with the Beckman glucose analyzer (vertical columns). Glucose levels were divided into clinically significant zones. The gray squares represent agreement of glucose levels between the analyzer readings and the CGMS or meter readings.*

For approval by the U.S. Food and Drug Administration, the CGMS was tested on 62 patients with diabetes in a multicenter clinical trial, comparing sensor output with >9,000 fingerstick glucose measurements (11). HbA_{1c} levels ranged from 5.4 to 10.6% (mean 7.4). The average correlation coefficient between sensor measurements and blood glucose values was 0.92. Of the 169 times when the CGMS read low (<70 mg/dl), the Accu-Check Advantage meter confirmed a low reading in only 50 cases (30%). The CGMS was far more accurate when it read in target range (70–180 mg/dl) (93% agreement with meter category) or >180 mg/dl (70% agreement).

The CGMS sensor measures the amount of glucose in the interstitial fluid and then calculates the expected corresponding blood glucose level. The difference between plasma glucose and interstitial fluid glucose is not constant. There may be a brief lag time after meals when interstitial fluid is lower, until plasma glucose diffuses across the interstitial space and they equilibrate. During exercise, the interstitial fluid glucose levels may decrease more quickly than the plasma glucose level because the cells are consuming glucose rapidly. In general, however, differences between plasma glucose and interstitial fluid glucose have been reported to be relatively minor, with the lag time between them usually <10 min (12).

In the present study, CGMS inaccuracies occurred at nighttime, when patients were inactive and not eating. Although we cannot rule out alterations in the interstitial fluid/plasma glucose gradient during sleep, this was likely a calibration problem. The CGMS uses a calibration procedure based on a linear regression with a fixed intercept. To produce the most accurate calibration, at least four fingerstick values measured by meter are entered into the monitor each day. The correlation coefficient is range dependent, with more optimum calibration occurring when a wide range of fingerstick glucose levels are available. Persons with tightly controlled diabetes may not have a sufficient range of glucose levels for accurate calibration.

There are potential pitfalls to the current study. Only seven subjects were studied, and all were in exceptionally tight metabolic control. It may not be appropriate to generalize the results to patients with greater daily glucose excursion. Medtronic MiniMed has recently released software with a new calibration method that may improve the accuracy of CGMS reporting. A larger study of patients with varying levels of glycemic control using the new software must be undertaken to explore this issue.

In conclusion, this small study demonstrated inappropriately low reported nighttime glucose levels by the CGMS in six of seven adolescents and young adults with tightly controlled diabetes. Although there are many advantages to using the CGMS for achieving control of blood glucose levels, reports of nighttime hypoglycemia should be interpreted with caution in patients with tightly controlled diabetes.

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