Analysis of Glucose Responses to Automated Insulin Suspension With Sensor-Augmented Pump Therapy

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OBJECTIVE—The advent of sensor-augmented pump therapy with a low-glucose suspend (LGS) function (Medtronic Paradigm Veo System), allowing insulin to be automatically suspended for up to 2 h when sensor glucose falls below a preset threshold, has the potential to reduce the duration of hypoglycemia. In this article, we analyzed blood glucose profiles following a full 2-h insulin suspension activated by the LGS function, as well as examined different patterns of use among patients.

RESEARCH DESIGN AND METHODS—Data from a cohort of participants using the Veo System for up to 6 months were analyzed to determine the time and duration of insulin suspension activated by the LGS function. We further evaluated overnight suspend events with no patient response occurring prior to 3:00 A.M., which allowed us to determine the pattern of sensor glucose values with no patient intervention during and after the period of insulin suspension.

RESULTS—There were 3,128 LGS events during the 2,493 days evaluated. The median duration was 11.2 min, and 36% of events occurred overnight. There were 126 full 2-h suspend events that occurred overnight with no patient response, occurring before 3:00 A.M. For these events, the mean sensor glucose at the end of the 2-h suspend period was 99 mg/dL (± 6 mmol/L). The mean sensor glucose 2 h after insulin delivery resumed was 155 ± 10 mg/dL (8.6 ± 0.6 mmol/L). There were no episodes of severe hypoglycemia or diabetic ketoacidosis.

CONCLUSIONS—Analyses of sensor glucose patterns following insulin suspension activated by LGS suggest that this technology is safe and unlikely to be associated with adverse outcomes.

Hypoglycemia is a common and serious complication of insulin therapy in children and adults with type 1 diabetes. Sleep poses a particular risk (1–3), and severe hypoglycemia is more frequent overnight (4). The advent of sensor-augmented pump therapy with a low-glucose suspend (LGS) function (Medtronic Paradigm Veo System; Medtronic Minimed, Northridge, CA), allowing insulin to be automatically suspended for up to 2 h when sensor glucose falls below a preset threshold, has the potential to reduce the duration of hypoglycemia and is a significant development toward full automation of insulin delivery in patients with type 1 diabetes.

Recently, Agrawal et al. (5) presented the first real-world use of the Veo and found that in patients who used the system for ≥3 months, LGS usage was associated with fewer sensor glucose values both <50 mg/dL and >300 mg/dL. In a user evaluation of the Veo, Choudhary et al. (6) found that LGS use was associated with reduced nocturnal duration of sensor glucose ≤40 mg/dL in patients in the highest quartile of nocturnal hypoglycemia at baseline.

Experience with the use of this technology is at an early stage, and reports are limited to few patients. We present our initial experience of the Veo in children and adults enrolled as part of an intervention trial using the Veo in individuals with impaired awareness of hypoglycemia. The data in this article were obtained from a subset of participants from the larger trial, which is still ongoing. In this article, we have focused on an analysis of the blood glucose profiles following the full 2-h insulin suspension and also have examined the different patterns of use among patients and their behavioral responses to alarms.

RESEARCH DESIGN AND METHODS—Participants aged between 4 and 50 years with type 1 diabetes on insulin pump therapy with impaired awareness of hypoglycemia participated in a 6-month intervention trial comparing standard pump therapy (insulin pump only) to the Veo (insulin pump with continuous glucose monitoring and LGS function). Hypoglycemia awareness was determined with the use of the modified Clarke’s questionnaire (7), with a minimum score of 4 suggestive of impaired awareness of hypoglycemia.

Participants randomly assigned to the Veo received a 3-h standardized face-to-face education session followed by ongoing patient-led assistance from an educator and doctor via phone or e-mail, together with scheduled visits every 3 months. We used Medtronic SOF-sensors for continuous glucose monitoring. Participants uploaded their pumps to the CareLink Therapy Management System website weekly, allowing evaluation of patient use and patterns of insulin suspension.

The LGS threshold was set at 60 mg/dL for study participants. As the sensor glucose falls below this level, the pump will alarm. If the patient does not respond to the alarm, insulin delivery will be suspended for up to 2 h, after which standard basal insulin is resumed. The patient may intervene...
at any stage throughout this 2-h period to resume insulin delivery. If there is no patient response, the pump will cycle in a continuous 6-h cycle of 2 h of insulin suspension followed by 4 h of basal insulin delivery.

In addition to the LGS alarm and suspend function, a low glucose alert was set at 70 mg/dL. At this level, the pump emits an audible sound or vibratory alert only but does not automatically suspend insulin. A high glucose alert also was set at 324 mg/dL for all participants.

Participants were requested to check for blood ketones if the first morning finger stick blood glucose level was ≥270 mg/dL and record the level of ketones, either with a diary or via e-mail to study personnel. Ketosis was defined as a blood ketone level of ≥0.6 mmol/L.

Data analysis
Data regarding sensor glucose values were obtained from the Carelink pump upload. An LGS event was defined as an episode of insulin suspension activated by the LGS alarm set at 60 mg/dL. For each individual subject, each LGS event was evaluated to determine the time and duration of each event; sensor glucose before, during, and after the period of insulin suspension; and corresponding meter blood glucose entered as a calibration before or after the event. For each 2-h LGS event, the event was further evaluated in terms of patient response. For instance, if a patient has responded to the audible alarm and elected to continue insulin suspension, this was considered to be an LGS event with patient response. If a patient has not responded to the audible alarm at all during the entire 2-h duration of insulin suspension, this was considered to be an LGS event with no response. These data then were collated to determine frequency and duration of all LGS events. We then further evaluated overnight LGS events with no patient response occurring before 3:00 A.M., which allowed us to determine the pattern of sensor glucose values with no patient intervention during and after the period of insulin suspension. The overnight period was defined as 8 h between 10:00 P.M. and 6:00 A.M.

RESULTS—Twenty-four participants were commenced on the system ([mean ± SD] aged 17.4 ± 9.3 years, duration of diabetes 8.7 ± 6.4 years, and duration of pump therapy 3.8 ± 3.0 years), with a median duration of use of 89 days (range 9–211). All participants had impaired hypoglycemia awareness, with a Clarke’s questionnaire score ≥4. The incidence of severe hypoglycemia for this cohort of 24 participants was 45.8 events per 100 patient-years prior to commencement of the Veo System. The mean A1C at baseline was 7.8 ± 0.9%. This improved to 7.4 ± 0.6% at 3 months (P = 0.015) while using the system. The A1C, however, increased from 3 to 6 months to 7.7 ± 0.9% (baseline vs. 6 months, P = 0.517) for the remainder of the intervention phase. The mean hypoglycemia unawareness score at baseline was 5.6 ± 1.3, which decreased to 4.5 ± 1.9 (P = 0.019) at the end of the 6-month intervention phase.

In total, the system was worn for 2,493 of 4,218 patient-days. The median percentage of sensor use was 72%. During the 2,493 sensor days evaluated, 3,128 LGS events occurred (1.3 events per day). The duration of LGS events was as follows: 13% (406) lasted the full 2-h duration, 12% (376) lasted between 1 and 2 h, 13% (400) lasted between 30 min and 1 h, 14% (446) lasted between 10 and 30 min, and 48% (1,488) lasted <10 min. The median duration was 11.2 min. Thirty-six percent of all events occurred overnight. Following the end of the main 6-month intervention phase, 79% of patients chose to continue wearing the system for an additional 6 months. In this cohort, two participants (8%) were not able to tolerate the system and discontinued using the system after several weeks.

Overnight full 2-h insulin suspend events
Of the full 2-h suspend events, 80% (n = 324) occurred overnight. In 168 (52%) of these nocturnal events, the patient responded to the alarm and elected to continue insulin suspension. In this case, the pump continued insulin suspension and automatically resumed insulin delivery at the end of the 2-h period. In the remaining 156 (48%) nocturnal events, there was no response from the patient despite an alarm of 60 dB lasting 20 s occurring every 2 min during the 2-h period.

A total of 126 (81%) overnight suspend events that were associated with no patient response occurred before 3:00 A.M. Analysis of these events allowed the evaluation of sensor glucose patterns 4 h following 2 h of insulin suspension and 2 h of basal insulin resumption without the influence of additional insulin therapy or carbohydrate intake (Fig. 1). Insulin was always suspended if there was no patient response and sensor glucose dropped

![Figure 1](attachment:image.png)
below 60 mg/L. As shown in Fig. 1, the fall in sensor glucose was arrested promptly after insulin suspension. The sensor glucose rose steadily thereafter in the 2-h period following insulin suspension. The mean sensor glucose at the end of the 2-h suspend period was 99 ± 6 mg/dL (\(99 ± 6\) SE = 5.5 ± 0.3 mmol/L). The mean sensor glucose 2 h after insulin delivery resumed was 155 ± 10 mg/dL (8.6 ± 0.6 mmol/L). The first-morning meter glucose entered into the pump following these events was 185 ± 9 mg/dL (10.3 ± 0.5 mmol/L). This was entered at the median time of 7:26 A.M. the following morning. The corresponding mean first-morning sensor glucose values was 144 ± 9 mg/dL (8.0 ± 0.5 mmol/L). The mean difference between sensor and meter glucose values was 41 mg/dL (2.3 mmol/L).

**Frequency of overnight full 2-h suspend events in individual participants**

The frequency of overnight full 2-h suspend events in individual participants is shown in Table 1. The frequency ranged from one event every 2.6 days (participant 22) to one event every 52.8 days (participant 11). Twenty-five percent of participants had one full 2-h suspend overnight at least once per week.

**Multiple LGS events**

Insulin was suspended for the full 2-h duration more than once overnight on 14 occasions, as shown in Table 2. During these occasions, the patient responded to the alarm and elected to continue insulin suspension. Insulin delivery resumed after 2 h of insulin suspension. After this time, the sensor glucose again fell below the LGS threshold of 60 mg/dL, and insulin delivery was again suspended.

On these occasions, insulin was suspended for an average of 4.2 ± 0.2 h overnight. The mean sensor glucose at the end of the suspended period was 112 ± 18 mg/dL (6.2 ± 1.0 mmol/L). Following these events, the mean first-morning meter glucose recorded in the pump was 239 ± 22 mg/dL (13.3 ± 1.2 mmol/L). The sensor glucose tended to read below the meter glucose by a mean difference of 115 mg/dL (6.4 mmol/L). There was no clear pattern in terms of sensor life. On waking, the difference in sensor and meter glucose values resulted in calibration error and in a subsequent request for insertion of a new sensor. These events were uncommon and represented 0.56% of sensor time evaluated.

**Adverse outcomes**

There were no episodes of severe hypoglycemia, defined as seizure or coma associated with hypoglycemia, during the time evaluated. There were no episodes of hospitalization for diabetic ketoacidosis. There were no events of hyperglycemia associated with ketosis following overnight suspend events.

**Table 1—Frequency of overnight 2-h LGS events in individual participants**

| Participant | Age (years) | LGS events (total) | LGS events (2-h duration) | Overnight LGS events (2-h duration) | Average days between each overnight 2-h LGS event |
|-------------|-------------|--------------------|--------------------------|-------------------------------------|-----------------------------------------------|
| 1           | 6.1         | 156                | 10                       | 10                                  | 13.4                                          |
| 2           | 7.7         | 5                  | 0                        | 0                                   |                                               |
| 3           | 8.8         | 78                 | 13                       | 10                                  | 13.4                                          |
| 4           | 9.2         | 149                | 3                        | 3                                   | 51.4                                          |
| 5           | 10.4        | 80                 | 15                       | 13                                  | 6.7                                           |
| 6           | 10.4        | 73                 | 13                       | 10                                  | 5.2                                           |
| 7           | 11.6        | 230                | 45                       | 25                                  | 6.9                                           |
| 8           | 12.4        | 161                | 54                       | 39                                  | 13.4                                          |
| 9           | 12.5        | 136                | 12                       | 9                                   | 11.7                                          |
| 10          | 13.3        | 56                 | 7                        | 7                                   | 9.0                                           |
| 11          | 13.6        | 146                | 5                        | 4                                   | 52.8                                          |
| 12          | 13.6        | 98                 | 3                        | 3                                   | 13.4                                          |
| 13          | 14.6        | 61                 | 1                        | 1                                   | 38.9                                          |
| 14          | 15.1        | 37                 | 3                        | 0                                   |                                               |
| 15          | 15.4        | 94                 | 20                       | 11                                  | 7.4                                           |
| 16          | 16.8        | 220                | 55                       | 37                                  | 4.9                                           |
| 17          | 17.2        | 69                 | 2                        | 2                                   | 39.7                                          |
| 18          | 21.0        | 122                | 24                       | 24                                  | 8.0                                           |
| 19          | 21.8        | 169                | 13                       | 13                                  | 10.0                                          |
| 20          | 26.7        | 136                | 16                       | 11                                  | 11.8                                          |
| 21          | 30.6        | 568                | 42                       | 42                                  | 5.0                                           |
| 22          | 31.7        | 253                | 44                       | 44                                  | 2.6                                           |
| 23          | 35.9        | 17                 | 2                        | 2                                   | 14.4                                          |
| 24          | 41.0        | 14                 | 4                        | 4                                   | 13.4                                          |

**Table 2—Multiple overnight LGS events**

| Event | Time of first LGS event (hh:mm:ss) | Duration (h) | Sensor glucose at the end of the final period of insulin suspension (mg/dL) | First-morning sensor glucose (mg/dL) | First-morning meter glucose (mg/dL) |
|-------|------------------------------------|--------------|--------------------------------------------------------------------------------|-------------------------------------|-------------------------------------|
| 1     | 1:27:05                            | 4            | 85                                                                             | 84.6                                | 356                                 |
| 2     | 0:37:55                            | 4            | 86                                                                             | 157                                 | 194                                 |
| 3     | 2:43:08                            | 4            | 194                                                                            | 200                                 | 293                                 |
| 4     | 0:51:06                            | 4            | 94                                                                             | 81                                  | 392                                 |
| 5     | 22:30:54                           | 4            | 84                                                                             | 54                                  | 234                                 |
| 6     | 22:51:09                           | 6            | 52                                                                             | 58                                  | 151                                 |
| 7     | 23:25:28                           | 4            | 194                                                                            | 85                                  | 169                                 |
| 8     | 22:29:22                           | 4            | 229                                                                            | 209                                 | 263                                 |
| 9     | 21:31:51                           | 4            | 14                                                                             | 40                                  | 160                                 |
| 10    | 0:36:49                            | 4            | 247                                                                            | 176                                 | 250                                 |
| 11    | 1:28:21                            | 4            | 112                                                                            | 148                                 | 290                                 |
| 12    | 1:00:29                            | 4            | 119                                                                            | 133                                 | 211                                 |
| 13    | 1:03:36                            | 4            | 151                                                                            | 160                                 | 275                                 |
| 14    | 1:56:39                            | 4            | 66                                                                             | 155                                 | 86                                  |
CONCLUSIONS—The LGS function was frequently activated in patients with type 1 diabetes with impaired awareness of hypoglycemia using sensor-augmented pump therapy. Most of these events were of short duration, whereby the patient has overridden insulin suspension and resumed insulin delivery. Almost 40% of all LGS events occurred overnight, and one in three events lasted the full 2-h duration. LGS events, including multiple activations, were not associated with severe hypoglycemia or diabetic ketoacidosis.

The overnight suspend events with no patient intervention provides a unique opportunity to evaluate the sensor glucose profile following full 2-h insulin suspension when the sensor glucose falls below 60 mg/dL. The initial fall in glucose levels was arrested promptly following insulin suspension and rose steadily during the 2-h suspended period. The mean glucose level at the end of the 2-h suspend event was 99 mg/dL, which is a near-normal value. The mean first-morning-meter glucose value entered into the pump was 185 mg/dL, and there was no associated ketosis. These analyses suggest that 2-h insulin suspension overnight is unlikely to be associated with adverse outcomes.

The pattern of overnight 2-h suspend events varied widely among our participants. The frequency of overnight full 2-h suspend events ranged from one episode every 2 months to one episode every 2–3 days in others. Patients having frequent overnight suspend events were surprised at the frequency of the events and indicated that they did not hear the alarms. Despite an auditory and vibratory alarm system to warn patients about hypoglycemia, patients are not responding to the current alarm systems. In a previous study evaluating the acoustic arousal threshold in adolescents with type 1 diabetes, we found that adolescents with type 1 diabetes could sleep through an alarm of 120 dB, which is equivalent to standing within 60 m of a jet plane at takeoff (8). These findings again indicate that alarm systems need to be further developed, perhaps to include a system based on varying frequencies and loudness to avoid acclimatization.

The finding of multiple activations of insulin suspension was previously reported by Danne et al. (9). We also found multiple activations on several occasions in our cohort. These events were uncommon; however, patients should be advised that this can occur if they respond to the LGS alarm and continue insulin suspension. This is easily done by pressing the ESC (escape) then ACT button on the pump. These steps effectively silence the LGS alarm and continue insulin suspension. In this case, the system considers this to be a patient response. Following insulin resumption at 2 h, if the sensor glucose again falls below the sensor threshold, LGS will again be activated and the 4-h basal insulin delivery cycle does not continue in this case.

Comparison of finger stick meter glucose and sensor glucose values suggest that the sensor tended to underread glucose values rather than overread them. There were no cases of sensor error resulting in failure to suspend and prolonged hypoglycemia during the night or in the morning. In the trial so far, there have been no episodes of prolonged nocturnal hypoglycemia resulting in seizure or coma, although we still are awaiting the final results. These results are in keeping with the reported accuracy data available for the Medtronic Veo System (10), in particular the low rate of false-negative alarms in the hypoglycemia range of <70 mg/dL.

Following 6 months of sensor-augmented pump therapy with the LGS function, there was no deterioration in A1C in this cohort. Hypoglycemia unawareness scores improved overall in this cohort. These findings are preliminary, and the final results will be reported at trial completion.

Acknowledgments—Insulin pumps and glucose sensors were provided by Medtronic via an unrestricted grant.

T.T.L. is supported by a Juvenile Diabetes Research Foundation postdoctoral fellowship and received travel reimbursement from Medtronic. T.W.J. received honoraria for scientific lectures and travel reimbursement from Medtronic, sanofi-aventis, Eli Lilly, and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

T.T.L. collected data, completed the analyses, and wrote the manuscript. J.A.N. and A.R. collected data and reviewed the manuscript. E.A.D. and T.W.J. reviewed the data and the manuscript. T.W.J. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented in abstract form at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011.

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