Safety of Nighttime 2-Hour Suspension of Basal Insulin in Pump-Treated Type 1 Diabetes Even in the Absence of Low Glucose

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Objective: An integrated sensor-augmented pump system has been introduced that interrupts basal insulin infusion for 2-hrs if patients fail to respond to low glucose alarms. It has been suggested that such interruptions of basal insulin due to falsely low sensor glucose levels could lead to diabetic ketoacidosis. We hypothesized that random suspension of basal insulin for 2-hrs in the overnight period would not lead to clinically important increases in blood β-hydroxybutyrate (BHB) levels despite widely varying glucose values prior to the suspension.

Research Design and Methods: Subjects measured meter blood glucose (BG) and BHB levels each night at 9PM and fasting the next morning. On control nights, usual basal rates were continued; on experimental nights, the basal insulin infusion was re-programmed for a 2-hr zero basal rate at random times after 11:30PM.

Results: In seventeen type 1 diabetes subjects (age 24±9yr, duration 14±11yr, A1c 7.3±0.5 [56mmol/mol]) BG and BHB levels were similar at 9PM on suspend (144±63mg/dL and 0.09±0.07mmol/L) and non-suspend (151±65mg/dL and 0.08±0.06mmol/L) nights (p=0.39 and p=0.47, respectively). Fasting morning BG increased following suspend nights compared to non-suspend nights (191±68mg/dL vs. 141±75mg/dL, p<0.0001) and the frequency of fasting hypoglycemia decreased the morning following suspend nights (p<0.0001). Morning BHB levels were slightly higher after suspension (0.13±0.14mmol/L vs. 0.09±0.11mmol/L, p=0.053) but the difference was not clinically important.

Conclusions: Systems that suspend basal insulin for 2-hrs are safe and do not lead to clinically significant ketonemia even if BG is elevated at the time of the suspension.
Introduction

The Diabetes Control and Complications Trial (DCCT) demonstrated a clear relationship between improved glycemic control and a decreased risk of diabetic complications but the ability to attain normoglycemia has been elusive for many patients living with type 1 diabetes (1,2). The DCCT also showed that the price that was paid for improved glycemic control with intensive treatment was a 3-fold increase in the risk of severe hypoglycemia (3). Hypoglycemia can lead to significant morbidity and mortality and fear of hypoglycemia is often a deterrent for patients and clinicians to achieve and maintain the strict target blood glucose levels employed in the DCCT (4).

Patients with type 1 diabetes are particularly vulnerable to severe hypoglycemic events while asleep at night (5). Unlike non-diabetic individuals, patients on fixed basal insulin replacement regimens are unable to automatically reduce insulin delivery and plasma insulin concentrations in response to falling plasma glucose levels. Since most patients with long-standing type 1 diabetes also lose the ability to mount a glucagon response to hypoglycemia (6), stimulation of epinephrine secretion is often the last line of defense to counteract the effects of insulin and to alert patients to low glucose levels (7). However, the release of epinephrine in response to hypoglycemia is markedly blunted during sleep at night in children and adults with and without diabetes (8,9). The Diabetes Research in Children Network demonstrated that the frequency of nocturnal hypoglycemia is increased 2-fold on nights following antecedent exercise (10) and continuous glucose monitoring studies have shown that low sensor glucose events at night are often prolonged (11). Indeed, in a case series, Buckingham and colleagues...
demonstrated that low sensor glucose levels were detected 2-4 hours prior to seizures in the middle of the night (12).

The introduction of new and improved sensor-augmented insulin pump systems has allowed a higher proportion of patients with type 1 diabetes to achieve target glucose and A1c levels with lower rates of severe hypoglycemia than in the DCCT (13-19). Moreover, such integrated systems offer the potential to “close the loop” of insulin administration by using computer algorithms to automatically adjust the rate of insulin infusion based on minute to minute changes in sensor glucose levels. Several studies have demonstrated the feasibility of this approach in inpatient clinical research center settings (20-29).

The first, relatively small step in the direction of a closed-loop system for outpatient treatment of type 1 diabetes has been achieved with the introduction of the Medtronic Paradigm Veo System (Medtronic Minimed, Northridge, CA). The low glucose suspend feature of this sensor-augmented pump system allows the basal rate of the patient’s pump to be automatically suspended for up to 2 hours if the patient fails to respond to the sensor’s low glucose alarms. Recent standardized inpatient protocols and unstructured outpatient clinical use studies showed that the low glucose suspend feature reduces the duration and severity of hypoglycemia without causing rebound hyperglycemia (30-34). In the recently published ASPIRE In-home study, which was a 3-month randomized, outpatient trial comparing the use of the low glucose suspend feature to sensor augmented pump therapy, threshold based pump suspensions led to a 30% reduction in nocturnal hypoglycemia without concomitant deterioration in glycemic control (35). Similarly, in the study by Ly et al. use of the low glucose suspend feature compared to pump-only treatment in a 6-month outpatient randomized trial led to a reduction in episodes of severe and moderate hypoglycemia(36) A potential concern related to the low glucose suspend
capability of sensor-augmented pumps is that suspension of basal insulin delivery for 2 hours because of a failing sensor when the blood glucose levels are not actually low might lead to hyperglycemia and ketoacidosis. To address this question, the present study was designed and implemented to evaluate the effects of random nighttime suspensions of basal insulin infusion rates for 2 hours even when blood glucose levels were not low.

**Methods**

**Study Subjects and Enrollment:**

Subjects were recruited from the Yale Type 1 Diabetes Program. Inclusion criteria included: age 15-50 years, clinical diagnosis of type 1 diabetes of at least one year’s duration; currently utilizing a Medtronic insulin pump to allow pump downloads to CareLink personal software or willing to use a Medtronic pump for the study period; duration of pump use of at least 3 months; HbA1c ≤9 % (75mmol/mol); BMI <95th percentile for age and gender; no other chronic medical condition (except treated hypothyroidism); on no medications (other than insulin) known to affect blood glucose levels; no episodes of severe hypoglycemia within three months of study participation and female subjects could not be pregnant or lactating. Subjects using sensor augmented pump therapy were permitted to take part in the study; however, during the study period, they were advised to not use their usual continuous glucose monitor to prevent alterations in care due to real-time sensor readings. All adult and pediatric subjects were required to have a responsible adult living in the same household who would serve as an alternate contact in the event of problems on basal suspension nights; these individuals were required to sign a study partner consent. After a complete explanation of the study protocol, written informed consent was obtained in subjects ≥18 years; in subjects <18 years, both an
adolescent assent and parent permission were obtained. The study was approved by the Yale University Human Investigation Committee.

**Study Procedures**

Following enrollment, subjects had a Medtronic CGMS® iPro™ Recorder (Medtronic Minimed, Northridge, CA) inserted for blinded sensor glucose data collection. Subjects were provided with a One Touch Ultra blood glucose meter (LifeScan Diabetes, Milpitas, California), a Precision Xtra meter (Abbott Diabetes Care, Alameda, CA), and urine ketone strips. They were instructed to check blood glucose, blood β-hydroxybutyrate, and urine ketone levels at 9p.m. on each study night and again the next morning prior to 8a.m while fasting before breakfast.

On each suspend night, one of the investigators called the subject to verify that pre-bed glucose and blood β-hydroxybutyrate levels were in acceptable ranges. Once verified, the investigator instructed the subject on which of the 6 randomized basal suspend patterns to use. All suspensions lasted for 2-hours with 0 unit/hr basal rates that started at 6 different times (11:30p.m., 12a.m., 12:30a.m., 1a.m., 1:30a.m., or 2a.m). For convenience, two of these patterns were pre-programmed into the pump at one of the study visits. Verification that suspends occurred as instructed was possible with downloads to CareLink.

In order to test compliance with the study protocol, blood glucose and ketone levels at 9 p.m. and fasting the next morning were obtained on 3-7 nights during the first week of the study without any 2-hour suspensions. These data were included in the analysis of non-suspend nights. During the next two weeks of the study, the patients received either their usual basal insulin doses (additional non-suspend nights) or one of the alternate basal rate profiles that included a basal rate of zero for 2 hours at random times starting between 11:30p.m. and 2a.m. (suspend
night data). Subjects and study staff were therefore not blinded to study condition. Throughout the study period, subjects wore a Medtronic CGMS® iPro™ Recorder (Medtronic Minimed, Northridge, CA) to gather blinded sensor glucose data.

On all study nights, subjects were instructed not to bolus after 9PM and to consume carbohydrate-containing snacks only if the 9PM blood glucose level was <100mg/dL. If blood glucose was >300mg/dL and/or blood β-hydroxybutyrate levels were >0.5mmol/L at 9 PM subjects were instructed to take a correction dose of insulin and any planned suspension was not performed. These nights were excluded from all data analysis.

*Data Analysis and Statistical Considerations:*

Blood glucose and blood β-hydroxybutyrate levels were compared during suspend and non-suspend conditions at 9PM and while fasting the next morning before 8AM. Data are expressed as mean ± standard deviation. Blood glucose and blood β-hydroxybutyrate levels were verified by meter downloads; CareLink uploads verified that subjects performed the suspensions as instructed and that no extra bolus doses of insulin were given in the overnight period on each of the suspend nights (Figure 1). Data collected from blinded continuous glucose monitors was used to assess changes in sensor glucose levels at the start of the suspend period (0hr), at the end of the suspend period (2hrs), and 4-hours after the initiation of the suspend period (4hrs). Non-suspend nights were chosen at random and matched within each subject to have the same time points analyzed.

Statistical comparisons betweensuspend and non-suspend nights were accomplished with unpaired t-tests. Post-hoc analysis included determination of the frequency of hypoglycemia in the morning before breakfast (defined as blood glucose <70mg/dL) with comparison of suspend
vs. non-suspend nights achieved using a Chi Square test. Calculations were performed using GraphPad Prism 6 (GraphPad Software, Inc. San Diego, CA).

Results

Nineteen subjects were enrolled into the study but two withdrew consent during the non-suspend week of data collection. The 17 subjects who completed the study were aged 24 ± 9 years (range 15-44) and had diabetes duration of 14 ± 11 years (range 4-34). Seven (41%) of the subjects were female. Subjects were generally well controlled with mean A1c 7.3 ± 0.5% (range 6.3-8.2) [56mmol/mol; range 45-66].

A total of 118 suspend nights (5-8 nights per subject) and 131 non-suspend nights (5-10 nights per subject) were included in the analysis. As demonstrated in Figure 2, mean 9PM blood glucose levels were similar on suspend (144±63mg/dL) and non-suspend nights (151±65mg/dL) and ranged between 32-281mg/dL on suspend and 40-294mg/dL on non-suspend nights. Nine P.M. blood β-hydroxybutyrate levels were also similar on suspend and non-suspend nights (0.09±0.07mmol/L vs. 0.08±0.06mmol/L, p=0.47).

Fasting blood glucose levels varied widely on suspend (range 39-368mg/dL) and non-suspend nights (39-372mg/dL). However, the suspension of basal insulin for 2 hours during the night resulted in mean fasting glucose levels that were 50mg/dL higher than on non-suspend nights (suspend 191±68mg/dL vs. 141±75mg/dL, p<0.0001). Blood β-hydroxybutyrate levels were slightly higher in the morning after suspension of basal insulin (0.13±0.14mmol/L vs. 0.09±0.11mmol/L non-suspend nights) but the difference did not reach statistical significance (p=0.053). Moreover, as shown in Figure 2, fasting blood β-hydroxybutyrate levels were >0.5mmol/L in only 5 suspend and 1 non-suspend nights (p=0.1); corresponding morning
urinary ketones ranged between trace to small on suspend nights and the urine ketone level was small on the one non-suspend night with a blood β-hydroxybutyrate level of 1.0mmol/L.

Sensor glucose data were collected during 99 suspend nights and 81 non-suspend nights. At the start of the suspend period, mean sensor glucose was 135±64mg/dL and ranged between 40-331mg/dL. As shown in Figure 3, sensor glucose rose by 18±58mg/dL by the end of the 2-hr suspension and by 55±73mg/dL 4 hours after the suspension. This differed significantly from the non-suspend nights, where baseline sensor glucose was 152±78mg/dL (range 40-400mg/dL) and no change in sensor glucose was appreciated at 2 and 4 hours (p=0.03 and <0.0001 respectively versus suspend nights).

As shown in Figure 4, 9PM blood glucose was <70mg/dL on 12% of suspend nights and on 10% of non-suspend nights (p=0.69). Notably, basal insulin suspension was associated with a reduced frequency of fasting hypoglycemia regardless of evening blood glucose with only 4% of pre-breakfast values <70mg/dL vs. 21% on non-suspend nights (p<0.0001). Additionally, sensor data documented 12 nights with sensor glucose <70mg/dL (mean 52±10mg/dL) at the start of the suspend period. Sensor glucose levels rose by 16±34mg/dL [0.9±1.9mmol/L] at 2-hrs and by 63±57mg/dL at 4 hours; in 83% of suspend nights sensor glucose was ≥60mg/dL 4 hours after basal insulin interruption. This differed from the 12 documented non-suspend nights with baseline sensor glucose <70mg/dL (mean 58±11mg/dL), during which sensor glucose levels at 2-hrs and 4-hrs were relatively unchanged, 65± 23mg/dL and 69±27mg/dL respectively (p=ns).

Discussion

This study was undertaken to evaluate whether 2-hr suspensions of basal insulin due to artifactually low sensor glucose values during the overnight period are safe, in the absence of
concurrent insulin pump or infusion site problems. We developed a study protocol that allowed us to evaluate this issue in a real-life, outpatient setting over a range of blood glucose levels and a large number of study nights. Even though we purposely did not wake subjects to measure blood glucose just prior to suspension of the basal infusion, the wide range of 9PM and fasting AM blood glucose values, as well as blinded sensor glucose levels, that were observed during the study serve to validate this approach. To eliminate the possibility of concurrent pump or infusion site problems, basal insulin suspensions were not carried out when the 9PM blood glucose was >300mg/dL or blood β-hydroxybutyrate level was >0.5mmol/L. Food intake was unrestricted until 9PM. However, the subjects were asked not to eat or to bolus after 9 PM in order to avoid masking the effects of the basal insulin suspend by taking extra insulin boluses during the night.

The major findings of the study support our hypothesis regarding the safety of 2-hr basal insulin suspensions during the overnight period. Even though there was a trend to slightly higher morning blood β-hydroxybutyrate levels after basal suspends, the 0.04 mmol/L difference compared to non-suspend nights was not statistically significant or clinically meaningful. Moreover, in 113 out of the 118 suspend nights, fasting blood β-hydroxybutyrate levels were within the normal range at <0.5mmol/L and the others were between 0.6-0.8 mmol/L. To put this finding into a more common clinical context, these blood levels resulted only in trace to small urinary ketone levels on the mornings following the suspension.

Our results are similar to those that were observed during a study from Attia et al (37). The Attia study was performed to describe the time course of metabolic deterioration in insulin pump patients following prolonged interruptions of basal insulin during the overnight period. In that study, mean blood β-hydroxybutyrate levels rose from 0.1 to 1.0 mmol/L after a 6-hr
suspension of the basal infusion of lispro insulin and as in the current study, the rise in mean blood β-hydroxybutyrate levels was <0.1mmol/L during the first two hours of basal insulin suspension. However, the Attia study involved only 9 subjects who were receiving lispro insulin during only one overnight stay in the clinical research center. Additionally, prior to basal insulin suspension, subjects in that study needed to be within a target blood glucose range of 60-150mg/dL. Thus, the results were far less convincing than our findings of minimal increases in blood β-hydroxybutyrate levels in 17 subjects over 118 nights with suspensions occurring at widely varying glucose levels. On the other hand, the number of subjects that were studied was relatively small. Thus, we cannot rule out the possibility that some patients may have exaggerated increases in blood ketone levels under the same conditions.

The ~50mg/dL increase in mean fasting glucose levels on suspend nights is consistent with the 30-45mg/dL increase in plasma glucose levels during the first 2 hours of basal insulin suspension in the Attia study (37). Our findings are also similar to the 30-65mg/dL increase in blood glucose levels reported in clinical research center and clinical use studies of the Medtronic Paradigm Veo system after a 2-hr basal insulin suspend (31-34). While not a primary outcome of the study, it is noteworthy that the random 2-hr basal insulin suspensions markedly decreased the frequency of fasting hypoglycemia the next morning.

Conducting a clinical trial in the outpatient setting like this poses a number of substantial challenges. Subjects may not follow the study protocol and may give bolus doses of insulin in the middle of the night, which, in turn might have minimized glycemic deterioration from the basal suspension. However, our use of the CareLink personal software program allowed for examination of every overnight period to assure basal suspension was programmed as instructed and that extra insulin was not delivered surreptitiously. It should also be noted that our cohort of
subjects was relatively well controlled, making them less susceptible to rapid deterioration when basal insulin infusion is interrupted. On the other hand, well controlled, intensively treated patients with type 1 diabetes are precisely the individuals who are likely to receive the greatest benefit of sensor-augmented pumps with low glucose suspend capability.

The main obstacle that must be overcome before closed-loop systems become a practical reality for the treatment of type 1 diabetes at home is to have redundant safeguards in place that will prevent the over delivery of insulin due to a system malfunction. Although automatically turning up insulin delivery to prevent hyperglycemia presents a potentially devastating safety risk, turning off a pump for a relatively short period of time to limit the extent and duration of hypoglycemia presents an attractive first step along the pathway to an artificial pancreas. Our demonstration of the safety of 2-hr suspension of basal insulin supports this approach and also sets the stage for the next step towards automatic control of glucose in type 1 diabetes; namely, automatically suspending basal insulin based on a projected low glucose level without sounding alarms.

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J.L.S researched data and wrote the manuscript. W.V.T. and S.A.W. researched data, contributed to the discussion, and reviewed and edited the manuscript. L.C., M.P.C., A.S., K.W., M.Z, E.T., C.M., and E.C. researched data and contributed to discussion. J.L.S. is the guarantor of this work and, as such, had full access to all 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 72nd Scientific Sessions of the American Diabetes Association in Philadelphia, PA June 2012, the 6th International Conference on Advanced Technologies and Treatments for Diabetes in Paris, France in February 2013, Translational Science 2013 in Washington, DC in April 2013, the American Society for Clinical Investigation and the Association of American Physicians Joint Meeting in Chicago, IL in April 2013, and the 73rd Scientific Sessions of the American Diabetes Association in Chicago, IL in June of 2013.

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Conflicts of Interest:

Medtronic Diabetes provided infusion sets, reservoirs, and loaner pumps to allow subjects not on Medtronic pumps to be recruited into the study. S.A.W serves as a consultant to Animas Corporation and received in-kind research support from Medtronic. W.V.T. serve as a consultant to Medtronic MiniMed and Animas Corporation. J.L.S., M.P.C., E.C., C.M., L.C., A.T.S, K.W, M.Z., and E.T. reported no potential conflicts of interest relevant to this article.

References:


**Figure Legends:**

**Figure 1. Verification of Suspension through Download of Insulin Pump**

Downloading subjects’ pumps onto CareLink Personal Software ensures that basal insulin suspension occurred as specified and that no surreptitious insulin delivery occurred in the overnight period. In this graph, basal insulin delivery in units/hr is listed on the left y-axis and noted by the horizontal lines, while bolus insulin delivery is on the right y-axis and depicted by vertical lines. Here suspension occurred between 2 and 4a.m.

**Figure 2. Before Bed and Fasting Blood Glucose and Beta Hydroxybutyrate Levels**

a) Pre-bed glucose levels (in mg/dL) on suspend vs. non-suspend nights were similar with a wide range of pre-bed glucose levels. b) Likewise, pre-bed beta hydroxybutyrate levels were equivalent in the two study conditions. c) As expected, blood glucose in the fasting period tended to be higher following nights with basal insulin suspension (p<0.0001). d) Fasting beta hydroxybutyrate levels tended to be higher in the fasting period following basal insulin suspension. Outliers are noted as closed circles. The dashed line at 0.9mmol/L is the upper limit of blood beta hydroxybutyrate levels associated with trace urinary ketones.

**Figure 3. Change in sensor glucose levels**

Change in sensor glucose value (in mg/dL) is compared on suspend (solid circles with solid line) to non-suspend nights (open boxes with dashed line). Sensor glucose levels at the start of a suspend period (0hr), the end of the suspend period (2hr), and 4-hrs after the initiation of a suspend period (4hr) are noted. On non-suspend nights, sensor glucose levels were assessed at time periods that would coincide with suspend nights (i.e. 11:30p.m.-1:30a.m. or 2a.m.-4a.m.).

**Figure 4. Frequency of Hypoglycemia**

Pre-bed and fasting blood glucose were classified based on whether or not hypoglycemia was present (blood glucose <70mg/dL). The non-suspend study condition is noted by grey bars. The percent of blood glucose levels <70mg/dL is represented on the y-axis.
Insulin Delivery

Basal Units / Hour

Pump Alarm  Bolus  Square Bolus  Basal

Tue 12:00a  2:00a  4:00a  6:00a  8:00a  10:00a  12:00p  2:00p  4:00p
P.M. Pre-Bed Glucose Levels

- Suspend Nights
- Non-Suspend Nights

Blood Glucose (mg/dL)

- p=0.39

A.M. Fasting Blood Glucose

- Suspend Nights
- Non-Suspend Nights

Blood Glucose (mg/dL)

- p<0.0001

P.M. Pre-Bed Beta Hydroxybutyrate Levels

- Suspend Nights
- Non-Suspend Nights

Beta Hydroxybutyrate (mmol/L)

- p=0.47

A.M. Fasting Beta Hydroxybutyrate Levels

- Suspend Nights
- Non-Suspend Nights

Beta Hydroxybutyrate (mmol/L)

- p=0.053
Δ in sensor glucose (mg/dL)

Time (hrs)

- Suspend
- Non-Suspend

p = 0.03

p < 0.0001
Before Bed

Non-Suspend

Fasting

% of blood glucose <70mg/dL

p=0.68

p<0.0001

Diabetes Care