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Prevention of Nocturnal Hypoglycemia Using Predictive Alarm Algorithms and Insulin Pump Suspension

Running Title: Prevention of Nocturnal Hypoglycemia

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Objective: The aim of this study was to develop a partial closed-loop system to safely prevent nocturnal hypoglycemia by suspending insulin delivery when hypoglycemia is predicted in type 1 diabetes (T1D).

Research Design and Methods: 40 **s**ubjects with T1D (age range # to #) were studied overnight in the hospital. For the first 14 subjects, hypoglycemia (<60 mg/dL) was induced by gradually increasing the basal insulin infusion rate (without the use of pump shut-off algorithms). During the subsequent 26 patient studies, pump shut-off occurred when either 3 of 5 (N=10) or 2 of 5 (N=16) algorithms predicted hypoglycemia based on the glucose levels measured with the FreeStyle Navigator® (Abbott Diabetes Care).

*Results***:** The standardized protocol induced hypoglycemia on 13 (93%) of the 14 nights. Using a voting scheme that required three algorithms to trigger insulin pump suspension, nocturnal hypoglycemia was prevented during 6 (60%) of 10 nights. When the voting scheme was changed to require only two algorithms to predict hypoglycemia to trigger pump suspension, hypoglycemia was prevented during 12 (75%) of 16 nights. In the latter study there were 25 predictions of hypoglycemia due to some subjects having multiple hypoglycemia events during a night, and hypoglycemia was prevented for 84% of these events.

Conclusions: Using algorithms to shut off the insulin pump when hypoglycemia is predicted, it is possible to prevent hypoglycemia on 75% of nights (84% of events) when it would otherwise be predicted to occur.

Continuous glucose monitoring (CGM) represents the "third era" in diabetes management following the eras of urine glucose testing and (self monitoring) blood glucose (BG) testing. One of the important potential benefits of real-time CGM is the ability of these devices to alarm for hypoglycemia. However, a previous study showed that 71% of youth did not respond to hypoglycemic alarms during the night (1). Moreover, most severe hypoglycemic events in the Diabetes Control and Complications Trial occurred during sleep hours (2). Davis et. al. found 75% of hypoglycemic seizures in children to occur during sleep (3). Sovik reported that among patients under age 40 years who died over a 10-year period, 6% of the deaths were due to "dead-in-bed" syndrome (4), which in many cases likely was the result of severe nocturnal hypoglycemia.

The availability of CGM systems has allowed determination of the incidence of nocturnal hypoglycemia in the home environment. In a randomized trial evaluating daily CGM use over a six-month period in children and adults with T1D, 216 subjects used a CGM device for a total of 25,473 nights (5). The glucose level was ≤ 70 mg/dL on 25% of nights, ≤ 60 mg/dL on 15% of nights and ≤ 50 mg/dL on 8% of nights (unpublished data) (5). Similar or even higher frequencies of nocturnal biochemical hypoglycemia have been found in other studies (6-9).

In a previous report, we prospectively studied the prevention of daytime hypoglycemia using CGM, hypoglycemia prediction algorithms, and temporary discontinuation of insulin via continuous subcutaneous insulin infusion (CSII, insulin pump) (10). Hypoglycemia was prevented using a 90 minute pump suspension on 60% to 80% of days. Cengiz, et. al. (11) described automatic pump suspension using the proportional integral derivative (PID) algorithm during 34 hours of closed-loop automated insulin delivery on 17 patients. They were successful in preventing hypoglycemia (glucose <60 mg/dL) in 14 of 18 (78%) suspension episodes. The purpose of the present study was to extend our original observations to evaluate the prevention of nocturnal hypoglycemia using hypoglycemia prediction algorithms.

RESEARCH DESIGN AND METHODS

Subjects for this study were recruited at the Barbara Davis Center (Aurora, CO) and the Stanford Medical Center (Stanford, CA). The protocol was approved by the local institutional review boards, and all subjects and parents or guardians signed an informed consent form and an assent form if necessary. Subjects in this study had been diagnosed with type 1 diabetes for at least one year and had used a downloadable insulin pump for at least three months.

Participants were trained on the use of the FreeStyle Navigator® Continuous Glucose Monitoring system (Abbott Diabetes Care, Alameda, CA) and instructed to wear two systems for each study. The two CGM systems were usually inserted one to two days prior to admission. Subjects arrived to the Clinical Translational Research Center (CTRC) at approximately 7:30pm after a dinner consisting of known amounts of carbohydrate, protein and fat.

Inducing Nocturnal Hypoglycemia: Fourteen subjects completed the control (hypoglycemia induction) visit at the CTRC with the intent to establish a consistent method for inducing nocturnal hypoglycemia using increases in basal insulin. Following admission to the CTRC and stabilization, the basal insulin was increased in 5 to 25% increments every 90 minutes, depending on the current BG, the glucose rate of change, and the linearly predicted glucose value to be

reached by 5:00 am (aim <60 mg/dL). The subject's BG was monitored every 15 to 30 minutes using the FreeStyle meter built into the Navigator (the only meter used in this study). Blood was also collected for YSI (Yellow Springs Instruments, Yellow Springs, OH) glucose analysis once the FreeStyle reading was <70 mg/dL. Once the hypoglycemic threshold was reached (BG value <60 mg/dL), oral carbohydrates were given to return glucose levels above 70 mg/dL.

Preventing Hypoglycemia: The same consistent method for inducing hypoglycemia was utilized in the subsequent studies to assess if hypoglycemia prediction and insulin pump suspension could prevent nocturnal hypoglycemia. The Navigator glucose alarms, including the built in Projected Low Alarm, were not activated during the study. For the hypoglycemia prevention studies, one of the Navigator sensors was connected to a laptop computer containing the Artificial Pancreas System (APS) (12) and the Hypoglycemia Prediction Algorithm (HPA) (13) composed of five separate prediction algorithms and a voting schema, briefly explained below.

1) Modified Linear Prediction Alarm (LP) – This alarm uses a 15 minute linear extrapolation and an uncertainty threshold based on the standard deviation of the glucose measurements in the previous 15 minutes.

2) Kalman Filtering – A Kalman Filter is used to obtain an estimate of glucose and its rate of change, which are then used to make predictions of future glucose levels. The filter is tuned to choose between the probabilities that a measured glucose change is real versus the result of signal noise (14).

3) Adaptive Hybrid Infinite Impulse Response Filter (HIIR) – An Infinite Impulse Response Filter updates parameters adaptively using the CGM signal. The HIIR filter considers a bandwidth of past data to update the filter parameters.

4) Statistical Prediction (SP) – Multiple empirical, statistical models are used to estimate future glucose values and their error bounds. A probability of hypoglycemia is generated and thresholded to produce an alarm (15).

5) Numerical Logical Algorithm (NLA) – Transmits a three point calculated rate of change and the current value into logical expressions to detect impending hypoglycemia. NLA provides insensitivity to sensor signal dropouts.

The algorithms for pump suspension were based on a 35 minute prediction horizon (looking 35 minutes into the future), and a glucose threshold of 80 mg/dL. The glucose threshold and 35 minute prediction horizon were chosen to allow time for the pump suspension to be effective in lowering insulin levels once the basal rate was suspended and was based on analysis of previous CGM data with nocturnal hypoglycemia. There is a sustained negative rate of change in glucose levels lasting a mean of 75 minutes after insulin pump suspension (10). In our initial 10 patient-studies we required three of the hypoglycemia prediction algorithms to be simultaneously positive twice in a 10-minute window before the pump was suspended. In the subsequent 16 studies we only required two alarms to be simultaneously positive twice in a ten minute window. When the hypoglycemia prediction algorithm alarmed (on a computer outside the subjects room) study staff manually suspended insulin delivery from the pump using a 90 minute suspend protocol.

Serum ketones were measured at the pump suspension, after insulin restart, and each morning on completion of the study using the Precision Xtra® meter (Abbott Diabetes Care, Alameda, CA).

Criteria For Restarting Insulin Infusion: The initial protocol involved a 90 minute pump suspension when hypoglycemia was predicted. Because there were often

multiple hypoglycemia events predicted each night, it was desired to limit the time insulin was suspended once the glucose was past the nadir. Thus, for the final 11 subjects the criteria for restarting a pump suspension included: 1) a minimum of 30 minutes of pump suspension, 2) a positive rate of change on the FreeStyle Navigator system of greater than 0.5 mg/dL-min, and 3) a FreeStyle Navigator glucose greater than 80 mg/dL. When basal insulin was restarted, it was at the subject's usual rate for that time of night.

RESULTS

Inducing Nocturnal Hypoglycemia: Fourteen subjects, ages 13 to 39 years, were initially studied for the induction of nocturnal hypoglycemia in the CTRC. Many of these same subjects participated in the subsequent two hypoglycemia prevention protocols. The demographic information for subjects participating in each of the three studies is shown in Table 1. The first study was designed to develop a reliable method of producing nocturnal hypoglycemia (>80% success) and the second and third studies were to study the possibility of preventing nocturnal hypoglycemia using predictive algorithms and temporary insulin suspension.

Using the protocol to generate nocturnal hypoglycemia, 13 of the 14 subjects (93%) reached glucose levels ≤60 mg/dL; 9 of 14 were <55 mg/dL. The mean increase in basal rate was 180%. There were no seizures or loss of consciousness.

Preventing Hypoglycemia: Twenty-six subjects participated in this phase of the study. A hypoglycemic threshold of 80 mg/dL and a prediction horizon (the time the algorithm is looking into the future to predict hypoglycemia) of 35 minutes was used for this study. For the first 10 patient-studies, the insulin pump shut-off occurred when 3 algorithms predicted hypoglycemia and for the last 16 patient-studies only 2 of 5 prediction algorithms were required to shut off the pump. During the first 10 subjects, hypoglycemia was prevented on 6 (60%) of the nights. There were a total of 15 hypoglycemic events predicted during these 10 nights (three subjects having two events, and 1 subject having 3 events) and hypoglycemia was prevented for 71% of the events (Table 2).

When we assessed the time between two hypoglycemic prediction algorithms voting to turn off the pump and three algorithms voting to turn off the pump, there was a mean difference of 12 minutes. To provide more time for the pump shut off to be effective, we therefore conducted our next set of studies requiring only two of the five algorithms to predict hypoglycemia to trigger pump suspension. This resulted in hypoglycemia being prevented on 12 of 16 nights (75%) (Table 2). Four subjects had 2 events during the night, 1 subject had 3 events, and 1 subject had 4 events. For the 25 hypoglycemic events, hypoglycemia was prevented 84% of the time. Figure 1 illustrates a successful prevention of hypoglycemia utilizing two insulin suspensions during the night.

We also evaluated which alarms were contributing to the first, second and third votes to turn the pump off (Table 3). The linear prediction algorithm was the least likely to predict hypoglycemia. Otherwise, all of the algorithms played a significant role in contributing to the vote.

Factors Relating To Successful Hypoglycemia Prevention: A comparison was done between several factors that may play a role in the success of the system. These included the accuracy of the FreeStyle Navigator system (a comparison of the FreeStyle Navigator system value to the YSI blood glucose value), the rate of change in the glucose readings at the time of pump suspension, and the YSI blood glucose value at the time of pump suspension. The difference between the FreeStyle Navigator

system and the YSI glucose values at the time of pump suspension was 4 ± 9 (mean ± SD in mg/dL) for successful events and the Navigator was always reading higher than the YSI when the predictive pump shut-off failed (mean of 18 ± 10 mg/dl for failures) ($p = 0.001$). The other factors, such as rate of glucose change and YSI glucose value at the time of pump shut off, were not significantly different between successful and unsuccessful events. The first episode of pump suspension was successful 75% of the time and subsequent episodes were successful 80% of the time. The glucose rate of change was less with subsequent pump suspensions, since the basal rate was returned to the usual infusion rate for that time of night (mean±SD rate of change = -0.72 ± 0.42 mg/dL-min on first shut off and was -0.24 ± 0.13 mg/dL-min on subsequent shut offs.

Early Restart Of Basal Insulin: In the last 11 patient-studies an early restart of basal insulin was permitted once the glucose was past the nadir (see Methods). There were 19 hypoglycemic events on these 11 nights and the early pump restart occurred on five occasions. The mean peak glucose following restart of an insulin infusion in the cohort of 11 subjects using an early restart was 149 (±32) mg/dL and the maximum glucose was 210 mg/dL. In the nights where an early restart of insulin was not permitted, the mean peak glucose following pump suspension was 158 (±50) mg/dL and the highest glucose was 275 mg/dL. These differences were not statistically significant.

Occurrence Of Ketonemia: Four subjects developed ketone levels >0.3 mM/L (range 0.4-1.5 mM/L). In each instance, when the serum ketones were checked several hours later, they were <0.3mM/L. In two instances the pump had been suspended for 90 minutes (final glucose levels 146 and 155 mg/dl) and in two instances (with more than one suspension) the pump had been suspended for a total of 180 minutes (final glucose levels 202 and 261 mg/dl). In each case the serum ketones were <0.3 mM/L after the first suspension. There were no clinical symptoms such as upset stomach, nausea, or Kussmaul respirations and no specific treatment was given.

CONCLUSIONS

Prevention of severe nocturnal hypoglycemic events remains one of the most challenging goals in the treatment of diabetes. With the prevention of severe hypoglycemia, it is likely that more people would be able to move toward optimal glycemic control. Due to the decrease in counterregulatory hormone secretion during sleep, even in people without diabetes (16), and the frequent loss of counterregulatory hormone secretion in people with diabetes (17; 18), prevention will likely require the use of a closed-loop system. In this initial step towards a closed-loop system, we tested the use of a subcutaneous sensor signal to predict impending hypoglycemia and to trigger pump suspension. It was not possible to eliminate nocturnal hypoglycemia completely. However, hypoglycemia was prevented during 75% of the nights and for 84% of predicted events. Presumably, a hypoglycemia prediction algorithm, as used in the present study, will be combined with discontinuation of CSII at a specific glucose level. The latter currently occurs in the Medtronic MiniMed Paradigm® Veo™ Real-Time System in Europe. The two working together might be very effective in preventing severe hypoglycemia.

In some cases for which hypoglycemia was not successfully prevented, the subjects' sensor glucose values were consistently running higher than the blood glucose values. This may have been due to CGM inaccuracy, or due to the known lag time of approximately 8-10 minutes between the two compartments (20). Future investigations might be able to use a forced CGM

calibration at bedtime if there is a significant discrepancy between a discrete bedtime glucose value and the sensor glucose to minimize this effect. We initially hypothesized that the rate of fall of the glucose values prior to a hypoglycemic event would also be a major factor in determining the success or failure of hypoglycemia prevention. However, this did not prove to be true.

In order to achieve a high rate of nocturnal hypoglycemia, we systematically increased nocturnal basal infusion rates until there was greater than an 80% risk of hypoglycemia. Because of receiving higher basal insulin infusion rates than on a typical night, subjects likely experienced a more rapid rate of fall in glucose levels, and had a longer residual insulin effect. This may have made it more difficult for the pump suspension algorithms to prevent impending hypoglycemia. Unfortunately, even when the basal rate was at the usual infusion rate for that subject (after the first pump suspension), we still failed to prevent hypoglycemia 20% of the time. It is known that once a person has had one hypoglycemic event, a second event is more likely (17). Thus, overall these results seem promising.

Although a rigid BG cutoff of <60 mg/dL was used to define failure of prevention of hypoglycemia, it is possible that we were overly cautious. The shortest known time of prolonged hypoglycemia (<40 mg/dL while using the Medtronic Paradigm CGM System) prior to a seizure is currently 2.25 hours (19). There were no severe hypoglycemic events in the current study. It would also be unlikely using the current protocol that the duration of hypoglycemia would be long enough to result in a severe hypoglycemic episode. Previous studies have shown that suspension of insulin delivery for up to two hours has not resulted in significant ketosis (10, 21-25). In our studies there was mild ketosis on four occasions when the pump was suspended for 90 to 180 minutes, and in each case serum ketones returned to normal with the reinstitution of basal insulin therapy.

Future studies will now need to begin in the home setting. Initial studies will be aimed at preventing nocturnal hypoglycemia, and will be randomized to include nights when the prevention system is in place, and to include control nights when the system is not in use. The bedside minicomputer will randomize the nights, and will also act as an intermediary (containing the prevention algorithms) between the insulin pump and the CGM. Studies will begin with adults but will then be extended to children. It is our belief that most episodes of severe nocturnal hypoglycemia using either this or a similar system will be preventable.

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Legend to Figure 1: Successful prevention of hypoglycemia (glucose levels by CGM or venous blood <60 mg/dL) as a result of two 90 minute periods of insulin pump suspension. The hypoglycemia prediction algorithm required 2 (of 5) alarms for pump suspension and were based on a 35 minute prediction horizon and a CGM glucose threshold of 80 mg/dL.

Table 1: Demographic information

	N	Age (yr) mean ± SD	Duration T1DM (yr) mean ± SD	HbA1c (%) mean ± SD	BMI mean ± SD
Study to induce hypoglycemia	14	21.0±7.5	12.1±6.0	7.8±1.9	22.0±3.1
Pump shut off requiring 3 predictions	10	22.5±6.3	12.7±5.5	7.3±0.8	24.6±2.8
Pump shut off requiring 2 predictions	16	22.0±8.9	11.5±6.9	7.3±0.7	25.2±3.9

Table 2: Results of the three alarm and two alarm voting systems

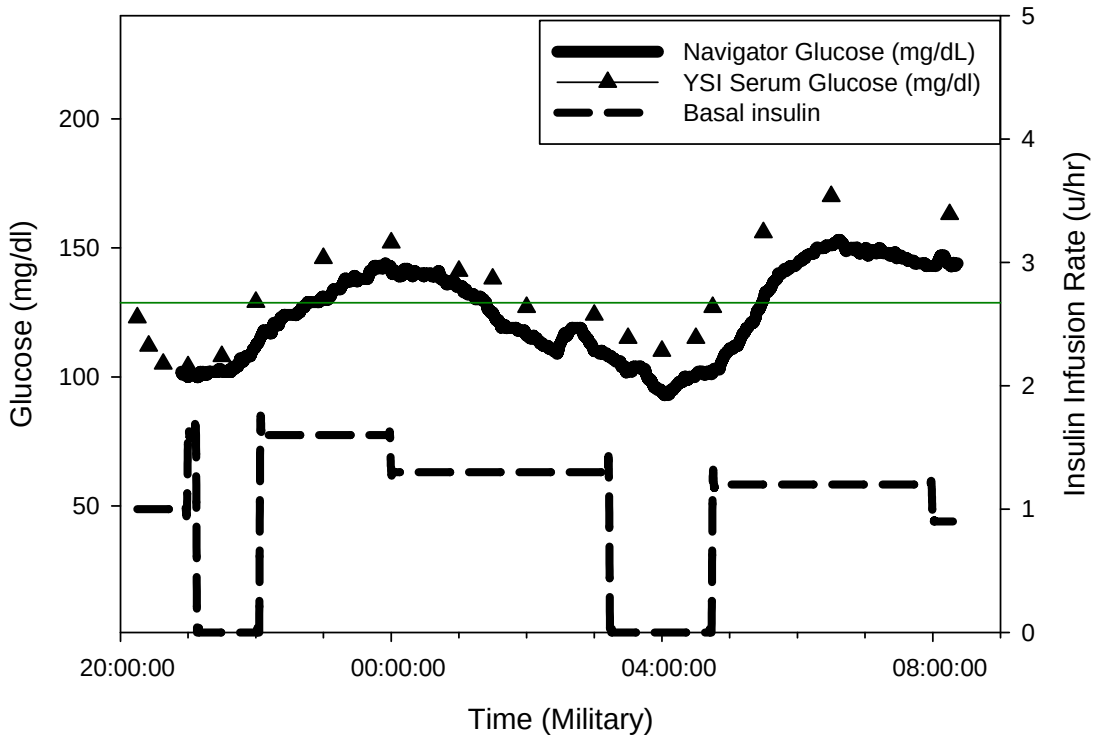
No. of predictive algorithms needed to trigger pump suspension	No. of subjects	% of subjects without hypoglycemia	No. of events*	% of events without hypoglycemia
3 of 5	10	60%	15	71%
2 of 5	16	75%	25	84%

* An event is an episode of predicted hypoglycemia resulting in a pump suspension.

Table 3: Distribution of algorithms that were the first, second or third to predict hypoglycemia.

Alarm	% of first alarms	% of second alarms	% of third alarms
Statistical Prediction	60	28	6
Numerical Logical	30	28	24
HIIR	3	10	49
Kalman	7	31	21
Linear Prediction	0	3	0

Figure 1.


Navigator Glucose (mg/dL)
YSI Serum Glucose (mg/dl)
Basal insulin
Glucose (mg/dl)
Insulin Infusion Rate (u/hr)
Time (Military)
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