Insulin Pump Therapy With Automated Insulin Suspension in Response to Hypoglycemia

Reduction in nocturnal hypoglycemia in those at greatest risk

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OBJECTIVE—To evaluate a sensor-augmented insulin pump with a low glucose suspend (LGS) feature that automatically suspends basal insulin delivery for up to 2 h in response to sensor-detected hypoglycemia.

RESEARCH DESIGN AND METHODS—The LGS feature of the Paradigm Veo insulin pump (Medtronic, Inc., Northridge, CA) was tested for 3 weeks in 31 adults with type 1 diabetes.

RESULTS—There were 166 episodes of LGS: 66% of daytime LGS episodes were terminated within 10 min, and 20 episodes lasted the maximum 2 h. LGS use was associated with reduced nocturnal duration ≤2.2 mmol/L in those in the highest quartile of nocturnal hypoglycemia at baseline (median 46.2 vs. 1.8 min/day, $P = 0.02$ [LGS-OFF vs. LGS-ON]). Median sensor glucose was 3.9 mmol/L after 2-h LGS and 8.2 mmol/L at 2 h after basal restart.

CONCLUSIONS—Use of an insulin pump with LGS was associated with reduced nocturnal hypoglycemia in those at greatest risk and was well accepted by patients.

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Continuous glucose monitoring (CGM) can reduce HbA_{1c} in type 1 diabetes (1–3). Despite the use of hypoglycemia alarms, most studies have not demonstrated a significant reduction in hypoglycemia, and prolonged nocturnal hypoglycemia occurs frequently (4). This may be because patients sleep through many of the alarms (5) and insulin delivery continues during hypoglycemia.

We report a user evaluation of the Paradigm Veo insulin pump (Medtronic, Inc., Northridge, CA), which can automatically suspend basal insulin delivery for up to 2 h in the event of CGM-detected hypoglycemia, thus reducing the duration of hypoglycemia.

RESEARCH DESIGN AND METHODS

—The Veo was evaluated by 31 patients (10 men) with type 1 diabetes (mean age, 41.9 ± 10.6 years) from six U.K. centers. Regional ethics committees approved the study, and patients provided informed consent. The Veo system has alarms for hypoglycemia, predicted hypoglycemia, rate-of-change of glucose, and, uniquely, a low glucose suspend (LGS) feature that is activated when sensor glucose reaches a glucose threshold set by the user. An alarm sounds, and if the user does not respond, basal insulin delivery is suspended for a maximum of 2 h, after which basal insulin delivery is resumed at the programmed rate. The patient may resume basal insulin delivery at any point.

During a 2-week run-in, CGM was used with only predictive, rate-of-change, high and low alerts active (LGS-OFF). LGS was then activated for 3 weeks (LGS-ON). We evaluated the response to LGS and compared hypoglycemia exposure and mean blood glucose during LGS-OFF and LGS-ON. Patients were divided into four equal groups (quartiles) by the duration of hypoglycemia during the run-in period, because we wished to test the hypothesis that those with the most hypoglycemia at baseline (without LGS) would have the greatest benefit with LGS. Hypoglycemia was defined as the lower limit of detection of the sensor (2.2 mmol/L) (6). The glucose threshold to trigger LGS was individualized (median 2.4 [range 2.2–3.5] mmol/L). Night was defined as 0000–0800 h. Treatment satisfaction questionnaires were completed at study end.

Data were compared using the Student *t* test, except for skewed data (hypoglycemia duration), which were compared with the Wilcoxon test. Values are mean ± SD or median (range).

RESULTS

—Two subjects withdrew during run-in due to difficulties using sensors, and one subject failed to activate the LGS. There were 166 LGS episodes in 25 of 28 (89%) completers (mean 1.9 LGS events/week), of which 76% occurred during daytime, and 55% were terminated within 10 min. LGS continued for the maximum 2 h in 20 episodes (12%), 75% of which were nocturnal. Of 20 completed 2-h suspends, 7 (35%) had no patient response throughout. In the remaining 13 (65%), patients responded to the alarm but elected to continue LGS for 2 h. Mean response time to the LGS alarm was longer at night compared with day (63.2 ± 8.2 vs. 17.4 ± 2.7 min, $P < 0.001$).

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LGS use was associated with significant reduction in the duration of nocturnal hypoglycemia (≤2.2 mmol/L) in those in the highest quartile of hypoglycemia duration at baseline: median 46.2 (36.6–191.4) vs. 1.8 (0.0–45) min/day (P = 0.02; LGS-OFF vs. LGS-ON) (Fig. 1) and mean 75.1 ± 54 vs. 10.2 ± 18 min/day (P = 0.02). Mean sensor glucose was not different with LGS-OFF or LGS-ON (6.4 ± 1.3 vs. 6.6 ± 1.1 mmol/L, P = 0.26). After the 20 complete 2-h LGS episodes, median sensor glucose was 3.9 (2.4–14.2) mmol/L at the restart of basal insulin and was 8.2 (3.3–17.3) mmol/L 2 h after restart. Carbohydrate ingestion was not recorded.

Concomitant (within 15 min of LGS) capillary glucose values were available for 43 of 166 episodes (25.9%) of LGS. These were >5 mmol/L in 13 episodes and >10 mmol/L in 4, although we do not know if any carbohydrate was ingested before testing. LGS was terminated within 2 min in all four episodes with capillary glucose >10 mmol/L, with sensor error alerts in two of these.

All subjects reported finding LGS "useful," and 93% reported feeling more secure at night, with reduced anxiety, and wanted to continue using it.

CONCLUSIONS—These data suggest that LGS has the potential to reduce nocturnal hypoglycemia in patients with type 1 diabetes at the highest risk. This is similar to results with insulin pump therapy providing the greatest reduction in hypoglycemia in those with the most hypoglycemia at baseline (7).

The risk of ketosis and hyperglycemia after the 2-h suspension of insulin delivery is low (8,9). In our study, median sensor glucose after 2 h of LGS was 3.9 (2.4–14.2) mmol/L. We could not determine if carbohydrate had been consumed during the LGS. There was no evidence of deterioration of overall glucose control with LGS activated.

Patients took longer to respond to the LGS alarm at night, and 75% of completed 2-h LGS events occurred overnight. This may relate to the combined effects of sleep and hypoglycemia on alertness/arousability, and reduced counterregulatory responses during sleep (10). Most daytime LGS episodes were terminated by users within 10 min.

The sensor may under-report glucose, particularly during nocturnal hypoglycemia and in view of the lag between interstitial and capillary glucose (11). Although the lowest displayed sensor value is 2.2 mmol/L, the Veo algorithm has improved hypoglycemia detection compared with previous algorithms, with a mean absolute relative difference between 2.2 and 4.4 mmol/L reduced from 24.8 to19.5% (12). We set the LGS threshold low (mean, 2.4 mmol/L), and a higher threshold may have led to greater reduction in hypoglycemia. Our study could not determine rates of false-positive LGS: 4 of 43 LGS had a capillary glucose reading within 15 min >10 mmol/L, and 2 of these were preceded by sensor error alerts. However, these capillary readings may be biased toward episodes when the patient thought the LGS was erroneous.

LGS reduces anxiety about nocturnal hypoglycemia. Randomized controlled trials that evaluate hypoglycemia and quality-of-life in type 1 diabetes using LGS pumps compared with insulin pump therapy alone, with or without CGM, are now needed. This is the first system that modulates insulin delivery in response to glucose levels without human intervention and is an important step toward clinically available closed-loop systems.

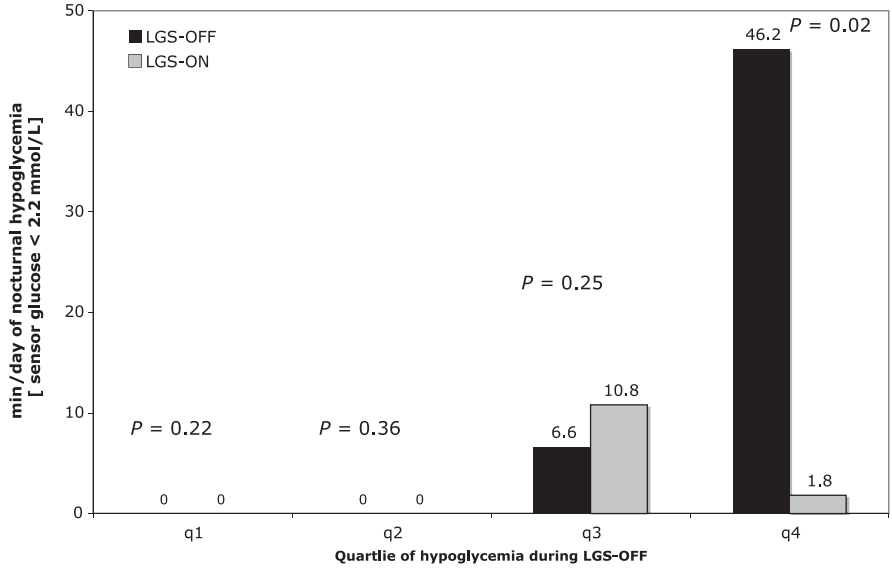

Figure 1—*Duration of nocturnal hypoglycemia (sensor glucose < 2.2 mmol/L) with and without LGS. The bars show median duration of hypoglycemia at night with LGS-OFF (black bars) and LGS-ON (gray bars) by quartile (q) of nocturnal hypoglycemia exposure at baseline.*

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