ORIGINAL ARTICLE

Insulin Pumps

John Pickup

Introduction

AS PREDICTED IN THE *ATTD 2011 Yearbook*, one of the main themes of the current year has been the publication of clinical experience and first trials of insulin pumps with automatic basal rate suspend in the event of hypoglycemia. These pumps are widely considered to be the first step toward a closed-loop insulin delivery system, and we include five studies on this topic in this chapter. Research continues on optimizing conventional continuous subcutaneous insulin infusion (CSII), particularly improving postprandial blood glucose increases, which are widely thought to be a major determinant of glycemic variability, and possibly a continued elevated HbA1c, on CSII. We include one of the few randomized controlled trials of the effectiveness of integrated pump bolus calculators, and then two articles on an emerging area of research: the value of including fat-protein, as well as carbohydrate counting, for calculating the insulin dose needed for a mixed meal. Finally, an article is included on a case series of patients with diabetic gastroparesis that shows the clinical value of switching from multiple daily insulin injections (MDI) to CSII in such patients.

EVALUATION OF A LOW-GLUCOSE INSULIN-SUSPEND PUMP

Insulin pump therapy with automated insulin suspension in response to hypoglycemia: reduction in nocturnal hypoglycemia in those at greatest risk

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Background

In spite of insulin pump therapy and continuous glucose monitoring (CGM), many patients with type 1 diabetes still experience troublesome nocturnal hypoglycemia, perhaps because they sleep through alarms. This study aimed to evaluate a sensor-augmented insulin pump with automatic low-glucose suspend (LGS) of the basal rate for up to two hours, designed to reduce the duration of hypoglycemia (Paradigm Veo, Medtronic Inc., Northridge, CA).

Methods

Subjects with type 1 diabetes (n=31) were recruited at six centers in the United Kingdom. After a two-week run-in period during which they were treated by CSII and CGM, but with the LGS feature turned off, subjects were then switched to a three-week period of CSII with LGS turned on. The CGM glucose threshold to trigger LGS was individualized (median 2.4 mmol/l).

Results

LGS events of any duration occurred mostly during the day (76%), of which 55% were terminated by the subjects within 10 min; 12% of episodes continued for the maximum 2 hr, 75% of which were nocturnal. LGS use was associated with reduced duration of nocturnal hypoglycemia (≤ 2.2 mmol/l) in those with the highest quartile of nocturnal hypoglycemia at baseline (1.8 min/day vs. 46.2 min/day, $p=0.02$). After 2-hour LGS, the median sensor glucose was 3.9 mmol/l at the restart of basal insulin and 8.2 mmol/l 2 hr after restart. 93% of subjects reported feeling more secure at night with reduced anxiety during LGS treatment.

Conclusions

An LGS pump was well accepted by patients and reduced the duration of nocturnal hypoglycemia in those at greatest risk. There was no evidence of deterioration of overall control when using LGS therapy.

Usage and effectiveness of the low glucose suspend feature of the Medtronic Paradigm Veo pump

Agrawal P, Welsh JB, Kannard B, Askari S, Yang Q, Kaufman FR
Medtronic Inc, Northridge, California
J Diabetes Sci Technol 2011; 5: 1137–1141

Background

The aim of this study was to analyze the use and efficacy in routine clinical practice of the Medtronic Veo LGS insulin pump from 2009, when it became available in Europe, to July 2010.

Methods

Data from 935 users of the Veo pump with type 1 diabetes in Europe were downloaded from the CareLink computer database. There were 49,867 patient-days when the LGS was turned on for 82% of the time, and a subset of 278 subjects was also analyzed, where the LGS was used for ≥ 3 months.

Results

Most LGS events occurred in the afternoon or evening. Most events lasted for <30 min (66%), with 45% <5 min (median duration 9.9 min). Maximal-duration events were 11% of the total and most occurred at night. Four hr after the onset of the maximal LGS, the mean sensor glucose was 150.1 mg/dl (8.3 mmol/l). In the subgroup, LGS usage reduced the percent sensor glucose readings <50 mg/dl (2.8 mmol/l) from 1.33% to 0.92% ($p < 0.001$), as well as the percent >300 mg/dl (16.7 mmol/l) from 4.6% to 3.4% ($p < 0.001$).

Conclusions

The LGS feature is turned on for most of the time by patients, but most events are terminated at <10 min. The exposure to hypoglycemia is reduced by LGS, but profound hyperglycemia after the suspend was not observed.

Prevention of hypoglycemia by using low glucose suspend function in sensor-augmented pump therapy

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Diabetes Technol Ther 2011; 13: 1129–1134

Background

Although CGM offers the possibility of avoiding hypoglycemia in diabetes, patients do not always react to alerts. The Paradigm Veo pump is equipped with automatic insulin shut-off (LGS) in the event of hypoglycemia. This study aimed to investigate the number, duration, and degree of hypoglycemic events associated with LGS pump use in children and adolescents.

Methods

Subjects with type 1 diabetes at three centers in Germany ($n=21$, aged 1–18 years) who were treated by CSII were studied for 2 weeks without LGS, and then switched to the LGS pump for 6 weeks. The LGS threshold was set at 70 mg/dl (3.9 mmol/l). In each study phase, data were analyzed using CareLink computer software.

Results

There was a mean of 6.2 LGS events/week, with 57% occurring during the day. Forty-two percent of LGS events were for <30 min, and 24% were for 2 hr (mostly at night). The mean frequency of hypoglycemic excursions <70 mg/dl (3.9 mmol/l) was reduced from 1.27 to 0.95/day ($p=0.01$), without a significant increase in mean glucose level (145 vs. 148 mg/dl, 8.1 vs. 8.2 mmol/l, LGS off vs. on). No severe hyperglycemia or ketoacidosis was observed).

Conclusions

The LGS pump is associated with a reduced frequency of hypoglycemia without compromising safety.

Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study

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Diabetes Technol Ther 2012; 14: 1–5

Background

Whereas previous studies have evaluated LGS pump use in a home setting with random everyday events that may predispose to hypoglycemia, the aim of this research was to measure the efficacy of the LGS after carefully monitored exercise.

Methods

Subjects with type 1 diabetes ($n=50$, aged 17–58) were randomized to an exercise session whilst treated with a Veo insulin pump, either with the LGS feature on (threshold set at 70 mg/dl, 3.9 mmol/l) or off, followed by crossover. Subjects were observed and samples taken for up to 4 hr after a blood glucose <70 mg/dl was recorded.

Results

The mean $\pm$ SD duration of hypoglycemia was less with LGS on than off (138.5 ± 76.7 vs. 170.7 ± 75.9 min, $p=0.006$). The mean end-of-study glucose was higher with LGS on (91.4 vs. 66.2 mg/dl, 5.1 vs. 3.7 mmol/l, $p < 0.001$). No end-observation plasma glucose was >250 mg/dl.

Conclusions

LGS treatment reduced the duration and severity of hypoglycemia induced by exercise without causing rebound hyperglycemia.

Analysis of glucose responses to automated insulin suspension with sensor-augmented pump therapy

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Diabetes Care 2012; 35: 1462–1465

Background

The aim of this study was to analyze blood glucose profiles from a cohort of subjects with type 1 diabetes who had been using the LGS pump for up to 6 months.

Methods

Patients with type 1 diabetes and hypoglycemia unawareness (n = 24, age 17 ± 9.3 years) used a Veo insulin pump for 6 months and uploaded data via CareLink. The time and duration of LGS events were recorded, including the overnight suspends with no patient response prior to 3 a.m.

Results

There was a mean of 1.3 events/day, with a median duration of 11.2 min. A minority of events occurred at night (36%). Full 2-hr suspend occurred mostly at night (80%) and was 13% of all events, with no response in 4% of the total; 48% of LGS events were <10 min. The mean glucose at the end of LGS was 99 mg/dl (5.5 mmol/l) and 155 mg/dl (8.6 mmol/l) 2 hr after insulin delivery was resumed. There were no episodes of severe hypoglycemia or ketoacidosis.

Conclusions

Insulin pump therapy with LGS is safe and unlikely to cause adverse outcomes.

Comment

Insulin pumps with automatic suspend of the basal rate in the event of CGM-assessed hypoglycemia have been in clinical use for about 3 years. Computer downloads are proving very valuable for assessing the efficacy and safety of the device, both in everyday use (e.g., Agrawal *et al.* and Ly *et al.*, discussed previously) and in trials (Chaudhary *et al.* and Danne *et al.*, discussed previously). There is remarkable consistency in the results of these studies, with general agreement that the frequency and duration of hypoglycemia during LGS pump treatment is reduced compared to conventional CSII plus CGM; most LGS events are deliberately cut short by the patient at <10 min

and occur during the day; full 2-hr events mostly occur at night (when the subject is asleep and unable to respond to the alert); and neither ketoacidosis nor excessive hyperglycemia post-suspend has been seen (mean glucose 2 hr after the basal rate was resumed was about 8.3 mmol/l, 150 mg/dl in the studies).

LGS pumps have been in use in Europe since 2009, and many thousands of patients have used them without significant mishap—a study published in abstract form, and updating that of Agrawal *et al.* above, reports on 7,810 EU patients (1); it can then be concluded that the system is both effective and safe. At the time of writing, LGS pumps were still not available in the United States.

The in-hospital study of Garg *et al.* above is valuable in that it carefully quantifies the duration and extent of the hypoglycemia reduction after exercise.

Judging by the satisfaction questionnaires in these studies, most subjects appear to like the LGS pump and use it for most of the time at home. What is now needed is a randomized controlled trial of the LGS pump vs. conventional CSII in those patients who are most likely to benefit: those with continued frequent severe hypoglycemia on optimized CSII.

BOLUS CALCULATORS AND FAT-PROTEIN COUNTING

Carbohydrate counting with a bolus calculator improves postprandial blood glucose levels in children and adolescents with type 1 diabetes using insulin pumps

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Pediatric Diabetes 2012; 13: 545–551

Background

Although bolus calculators to aid carbohydrate counting (CC) have been incorporated in insulin pumps for a decade or so, there have been no randomized controlled trials of their effectiveness in young people. Though CC is widely practiced in some countries, it is not in others such as Sweden.

Methods

Children and adolescents with relatively well-controlled type 1 diabetes (baseline HbA1c 7.6%) were studied at three centers in Sweden (n = 40, aged 5.0–19.5 years). They were receiving CSII for at least 6 months and had not previously practiced CC at recruitment and were randomized to three groups: A) traditional adjustment of meal insulin doses by estimated carbohydrate content; B) manual CC; and C) CC by pump bolus calculator. Patients in group A received traditional dietary education, those in B and C received dietary education in CC, based on insulin: carbohydrate ratios and correction factors. The study duration was 12 months.

Results

HbA1c did not differ among groups at the study end. The percent of post-meal plasma glucose levels in target (4–8 mmol/l) was highest in group C (30.6 vs. 35.6 vs. 55.3%, A vs. B vs. C, $p=0.025$). Hypoglycemia was reduced in all groups over the 12 months but did not differ between groups. There was a borderline decrease in plasma glucose standard deviation in group C ($p=0.056$) over the 12 months.

Conclusions

Bolus calculators can help reduce post-meal plasma glucose fluctuations and result in more postprandial glucose levels in the target range.

Benefit of supplementary fat plus protein counting as compared with conventional carbohydrate counting for insulin bolus calculation in children with pump therapy

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Pediatric Diabetes 2012; **13**: 540–544

Background

Conventional meal insulin adjustment is usually based on CC alone, but food with a high fat and protein content is known to cause relative insulin resistance and a prolonged blood glucose rise commencing 3–4 hours after meal ingestion. Modern insulin pumps have the option of delivering a number of bolus profiles, including dual waves that have been suggested for fat-protein-rich meals. This study compares CC with supplementary fat-protein counting (FPC), using either normal or dual-wave boluses.

Methods

Children and young people with type 1 diabetes who were being treated by CSII ($n=42$, aged 6–21 years) were randomized to eating a standard pizza-salami lunch meal (50% carbohydrate, 34% fat, 16% protein) on four different days with either normal or dual-wave (70% immediately, 30% over 2 hr) bolus using either CC alone or CC+FPC. CGM was used for glucose monitoring of the 6-hr post meal glucose profiles.

Results

For all test meals, sensor glucose values were lower for CC+FPC than CC alone between 3 and 6 hr. The area under the curve for glycemia was lower for CC+FPC than for CC alone, independently of the kind of bolus. Postprandial hyperglycemia (<70 mg/dl, 3.9 mmol/l) was more frequent with CC+FPC (35.7% vs. 9.5%, $p<0.001$).

Conclusion

Insulin dosage for meals based on both CC and FPC lowers postprandial glucose levels more than traditional CC.

Does the fat-protein meal increase postprandial glucose level in type 1 diabetes patients on insulin pump: the conclusion of a randomized study

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Diabetes Technol Thera 2012; **14**: 16–22

Background

The aim of this study was to compare the management of postprandial hyperglycemia after a mixed meal, when the meal insulin bolus is given as either the traditional normal wave, based on carbohydrate counting (CC) alone, or as a dual wave, based on CC plus fat-protein counting (FPC).

Methods

Type 1 diabetic subjects treated by insulin pump therapy ($n=24$) were randomized to eat a pizza dinner (45 g/180 kcal carbohydrate, 400 kcal fat-protein) with either a 6-hr dual-wave insulin bolus calculated as carbohydrate units ($=10$ g) $\times$ insulin carbohydrate ratio [ICR] (for the normal wave) + fat-protein units ($=100$ kcal) $\times$ ICR (for the extended wave), or to a normal wave with insulin calculated as carbohydrate units $\times$ ICR.

Results

In the group treated by a normal-wave insulin bolus and CC alone, the blood glucose levels after a mixed meal reached a peak at 4–6 hr postprandially. Blood glucose levels were lower in the experimental group with dual-wave bolus and FPC in addition to CC.

Conclusions

Mixed meals cause marked postprandial hyperglycemia after 4–6 hours, but a dual-wave bolus calculated from CC+FPC is effective at controlling glycemia.

Comment

Although bolus calculators are a feature of all the modern insulin pumps in widespread use, and have been used in clinical practice for 10 years, there is surprisingly little experimental evidence for their effectiveness. Shashaj *et al.* (2) have previously published an observational study that indicated lower postprandial glucose levels in those patients who use a bolus calculator, but the study of Enander *et al.* above is a useful randomized controlled trial that shows less glycemic variability and more postprandial glucose values in target when a bolus calculator was used. Interestingly, HbA1c did not differ between those using or not using the calculator. This may be because the subjects were relatively well controlled at baseline (7.6%), and as with other technologies, the greatest effect is likely to be in those with the worst control. Other limitations of this study are lack of information on bolus type, timing, and the amount of carbohydrates. There is still need for more careful studies of the effectiveness of bolus calculators.

Current bolus calculators are based on carbohydrate counting, both the amount of carbohydrate in the intended meal and the insulin:carbohydrate ratio for the individual. However, postprandial blood glucose levels are often inadequately controlled during usual pump treatment, and this may be a failure to take into account the additional and often substantial fat and protein content of many mixed meals. Kordonouri *et al.* and Pankowska *et al.* above both show the previously known late postprandial blood glucose increase after a pizza meal, which has been attributed to various mechanisms, including fat-induced insulin resistance and delayed gastric emptying, as well as protein-induced increased glucagon secretion. The logic of using a dual-wave bolus for such high fat/protein meals is to manage the carbohydrate content with a short normal wave and the late fat/protein-induced hyperglycemia with an extended wave. Pankowska *et al.* above supplies an algorithm for calculating the components of the dual wave based on CC and FPC.

Should FPC be introduced into clinical practice? There are likely to be many problems: how to estimate the fat and protein content in meals with reasonable accuracy, how to adapt bolus calculators to receive information on fat and protein, and the complexity.

CLINICAL INDICATIONS

The role of continuous subcutaneous insulin infusion therapy in patients with diabetic gastroparesis

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Diabetologia 2011; **54**: 2768–2770

Background

Gastroparesis (delayed gastric emptying) is a recognized complication of long-standing diabetes. About 10% of sufferers have upper gastrointestinal symptoms, such as abdominal discomfort or fullness, nausea and vomiting, and the mismatch between insulin absorption/action and food absorption typically leads to fluctuating glycemic control and frequent hypoglycemia with even optimized multiple daily insulin injections. This study reports on two center's experience with treating diabetic gastroparesis by insulin pump therapy (CSII).

Methods

The data from 26 type 1 diabetic patients diagnosed with gastroparesis by symptoms and established delayed gastric emptying on scintigraphic studies. Other structural abnormalities were excluded by abdominal ultrasound and upper gastrointestinal endoscopy. CSII was initiated with boluses

given as an extended wave. As symptoms improved, extended wave times were shortened or switched to a dual wave (10% first phase).

Results

During 12 months CSII, hospital admissions fell from a median of 8.5 (0–144) on MDI to 0 (0–15) days/patient/year on CSII ($p < 0.05$). HbA1c fell from a median of 9.8 on MDI to 8.0% on CSII ($p < 0.05$). Glycemic variability, as measured by the coefficient of variation of capillary blood glucose levels, was reduced from 0.57 on MDI to 0.37 on CSII ($p < 0.001$). Mean total daily insulin dose was reduced from 49.3 units on MDI to 33.7 units on CSII ($p < 0.005$).

Conclusions

Treatment of patients with diabetic gastroparesis resulted in improved HbA1c, glycemic variability, and insulin dosage.

Comment

Gastroparesis is thought to be a common cause of hypoglycemia in diabetes, so it is a pity that this study does not report changes in the frequency of severe and mild-to-moderate hypoglycemia when the patients were switched from MDI to CSII. Nevertheless, it is encouraging that the patients experienced such notable benefit from CSII, particularly for HbA1c and rate of hospital admission (which were reduced to a median of zero days/patient/year).

The mechanism of action of CSII in gastroparesis is probably mainly related to use of an extended meal-time bolus, which more effectively covers the delayed gastric emptying and matches timing of insulin absorption with food absorption. But the expected reduction in HbA1c and glycaemic variability, which is seen with general type 1 diabetic patients switched to CSII, may also contribute, since hyperglycemia is itself known to slow gastric emptying (3), and glycemic fluctuations worsen gastrointestinal symptoms (3).

Author Disclosure Statement

The author has received speaker and/or consultancy fees from Medtronic, Roche and Cellnovo, manufacturers of insulin pumps.

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