JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Diabetes and Endocrinology

Inrerventional Study

Continuous Glucose Monitoring Assessment of Glucose Variability with Liraglutide add-on or Substitution in T2DM during 24 hour and 3 hour Time-Periods

Paul M. Rosman, DO, Jeffrey S. Freeman*, DO, Jayme A. Aschemeyer, DO, David M. Capuzzi, MD, PHD,

Philadelphia College of Osteopathic Medicine, PA, USA

**Corresponding author: Dr. Jeffrey S. Freeman, DO, FACOI, FNLA, Professor and Chair, Division of Endocrinology, Department of Internal Medicine, Philadelphia College of Osteopathic Medicine 4170 City Avenue, Suite 324, Philadelphia, PA 19131, USA, Tel: (215) 871-1916; Fax: (215) 871-1928; Email: jeffreyfreemando@aol.com*

Received: 07-30-2015

Accepted: 09-16-2015

Published: 10-02-2015

Abstract

Background

Medication add-ons and substitutions used commonly to improve glucose management in people with diabetes may create unforeseen interactions that complicate patient care. We addressed this concern using Continuous Glucose Monitoring (CGM) from which we measured glycemic variability as a metric of successful add-on or substitution. Additionally, we compared calculated HbA1c differences between pre liraglutide and post liraglutide treatment mean 24 hour studies. Lastly, we looked at hypoglycemic predictability as a tool to evaluate patient safety when add-ons or substitutions occur.

Method

This single subject intervention series in 10 T2DM subjects tested the utility of CGM variability and calculated HbA1c changes before and after liraglutide addition or substitution as a measure of efficacy and hypoglycemic predictability as a measure of patient safety.

Results

The addition or substitution of liraglutide to other hypoglycemic therapeutics reduced mean glycemic variability, mean glucose and calculated HbA1c values. However, these differences were not statistically significant due to the small n in this group of subjects. Similarly, anticipating hypoglycemic susceptibility was unsuccessful because of the day-to-day changes in glucose rhythms.

Conclusion:

This small investigative series offers hints for follow up studies of glycemic variability effects of add-on or substituted agents in T2DM patients. These include a larger group of subjects, more consistency in timing of medical and looking at drug – drug interaction one at a time.

Introduction

Current ADA/EASD [1] and AACE/ACE [2] recommendations for T2DM care includes metformin as initial pharmacologic therapy followed by add-ons to achieve HbA1C targets. However, both safety and efficacy issues [3, 4] may confound the clinical impact of add-on pharmacotherapy. For example, hypoglycemia may occur with several add on medications and the timing of the hypoglycemia causing interaction may be different in different patients or even in the same patient on different days. Additionally, timing the desired benefit of an add-on medication may be difficult if meal content or times vary significantly.

This trial suggests CGM (continuous glucose monitoring) can improve safety and efficacy of add-ons or substitutions in T2DM patients by identifying adverse and beneficial responses. 24-hour CGM studies demonstrate clinical utility of add-ons or substitutions in Type 2 diabetes patients by identifying decreases in glycemic variability, allowing calculated HbA1c values derived CGM data, and identifying periods of hypoglycemic risk.

We compared CGM data before and after a single add on or substitution medication, liraglutide, in 10 type 2 diabetes patients on different regimens of treatment and compared 24 hour time frames with regard to glycemic variability, calculated CGM derived HbA1c changes and hypoglycemic risk before and after liraglutide therapy.

Patients, Methods and Statistical Analysis

Study Design

We used a descriptive single subject intervention trial design that highlights individual differences in response to independent variable effects. The trial was unblinded and non-randomized. Each patient served as his or her own control. This study design has three requirements, baseline, intervention and reversal [5, 6] Baselines were established using 2 to 6 consecutively repeated 24-hour CGM studies. The liraglutide treatment intervention followed the first, baseline, CGM and continued until we performed a second series of 2 to 6 consecutive CGM studies in each subject. We did not perform reversal of the liraglutide effect, since most patients' glucose levels improved on liraglutide. This suggested we could not rule out carry over effects from previously administered medication. However, the time lapse between the before and after CGM studies was prolonged enough to mitigate this concern.

Subjects

Inclusion criteria for subjects included T2DM diagnosis and age over 21. Exclusion from participation in the trial occurred if potential subjects took liraglutide before the trial, reported chronic musculoskeletal pain, developed CKD 4, 5, or 6, were legally blind, experienced acute coronary syndrome, congestive heart failure or respiratory failure, had gastroparesis or other painful gastrointestinal disorders, active urinary tract infections or known allergic or adverse reactions to other glucagon-like peptides. Prospective subjects had examinations for thyroid nodules that included questions regarding their family history of thyroid malignancy. All histories and neck examinations were negative in this regard. We measured no Calcitonin levels in the subjects.

The Study protocol and the informed consent approval came from the Institutional Review Board of the Philadelphia College of Osteopathic Medicine, Philadelphia, PA. Each patient in this study signed the informed consent statement after demonstrating clear understanding of the protocol and asking questions.

Ten subjects with T2DM with the following characteristics were studied: (Table 1) Ages: 41-70; Gender: 5 female, 5 male; medication: included metformin, Sulfonylurea, pioglitazone, DPP-4, exenatide, and insulin. The duration of diabetes: 4 months to 21 years. In addition, three patients had morbid obesity, six patients were obese and one patient was overweight. At the start of the study, HbA1C values ranged from 5.7% to 10.2%. Hemoglobin A1C levels calculated from each patient's average glucose levels after multiple CGM studies ranged from 6.5% to 10.9%. The difference in HbA1c was not significant at a 95% confidence level for the group using a non-parametric calculation.

Methods

Dexcom (San Diego, Ca.) glucose sensor studies were completed for 2 to 6 consecutive days before and 2 to 6 consecutive days after liraglutide. Liraglutide doses ranging from 0.6 to 1.8 mg subcutaneously was administered daily for 1-4 months at a maximum tolerated dose. The time of day liraglutide was given depended on the patient's preference; this was allowed based on the FDA approved prescribing information of liraglutide [7]. Tolerability criteria were based upon adverse reactions listed in the FDA approved prescribing information for liraglutide [7]. In subjects taking insulin, thiazolidinedione or sulfonylurea reduced or discontinued doses occurred before liraglutide was given, if hypoglycemia avoidance was clinically indicated.

We planned 120 CGM studies in these 10 subjects (60 before and 60 after liraglutide); 112 CGM studies were performed. We discarded 2 studies before liraglutide and 2 studies after liraglutide because of missing data, totaling 108 studies analyzed from patients; 54 studies before and 54 studies after starting liraglutide.

Missing Data due to glucose sensor dysfunction during CGM required application of the last value carried forward rule with a modification for CGM conditions. The modification required discarding entire 24-hour CGM studies that lacked more than 5% of the 288 data points expected for that day. If CGM was ongoing for less than a 24-hour day, which occurred when studies began or ended, we applied the 5%

rule, based on the expected number of data points during that day.

Hypoglycemic risk was estimated in each patient by taking the lowest glucose values and the time it occurred in each patient before and after liraglutide

c) Standard deviation in each patient's composite 24-hour study data was calculated as a measure of variability. Pre liraglutide findings were compared with those found after liraglutide administration [9-11]. Both for individual patients and for composite analysis and evaluated both visually and statistically.(See example in Figure 1).

TABLE 1: PATIENT'S CHARACTERISTICS BY INITIAL HEMOGLOBIN A1C

SUBJECTS	AGE (YEARS)	GENDER	WEIGHT (POUNDS)	BMI	DIABETES DURATION (YEARS)	STARTING HB A1C (%)(calculated	ENDING HB A1C (%) calculated	COMPARATOR MEDICATION	END METICATION	Change Type
JP	55	M	217	32.8	?	6.5%	6.0%	glyburide/metformin 5/500 Insulin glargine 100 U bid insulin aspart 6 U bid pioglitazone 45 mg /D	levemir 80 U SQ bid insulin aspart 6 U bid liraglutide 1.8 mg/D	Add-on
EF	60	f	327	53.5	13	6.5%	6.3%	metformin 1000 mg bid	metformin 1000 mg bid liraglutide 0.6 mg /D	Add-on
TM	57	F	248	45.	8	7.0%	6.7%	metformin 1000mg bid glimepiride bid	metformin 1000mg bid glimepiride bid liraglutide 1.8 mg /D	Add-On
RG	41	M	353	48	5	7.0%	7.6%-	metformin 500 mg /D saxagiptin 5 mg /D	metformin 500 mg /D liraglutide 1.8 mg/day	sub
SF	47	M	252	?	1.5	7.0%	7.4%	metformin 500 mg 2X/D glipizide XL 10mg 2X/D	metformin 500 mg 2X/D glipizide 10 mg 2X/D liraglutide 1.8 mg 1X/D	sub
GB	70	M	196	29	0.33	7.2%	7.2%	metformin 500 mg /D exenatide 10 mcg bid	metformin 500 mg /D liraglutide 1.8 mg /D	sub
CB	57	F	217	35	15	8.1%	6.1%	Glucophage XR 500 mg/d Amaryl 8mg/d Insulin glargine 30AM40 PM, insulin aspart sliding scale	liraglutide 0.6 mg/D Insulin glargine , insulin aspart sliding scale	sub
PS	56	F	204	33.4	?	8.4%	8.4%	human insulin 70/30 42 U AM/10 U PM pioglitazone 30 MG/D	human insulin 70/30 47 U AM/10 U PM liraglutide 1.8 mg /D	sub
JC	51	M	233	31.2	11	8.4%	6.4%	Insulin glargine 30 U AM/ 20 U PM insulin aspart 10-16 U by scale @ brkfst / 12-18 U by scale @ l &d	Insulin glargine 30 U AM/ U 20 PM insulin aspart 10-16 U scale liraglutide 1.8 mg /D	sub
MS	44	f	166	30.4	7	10.9%	9,2%	metformin 500 mg/D byetta 10 mcg 2x/D	metformin 500 mg/D liraglutide 1.8mg/D	sub

Statistical analysis

Statistical significance was accepted at the $p < 0.05$ level of probability for the null hypothesis using a non-parametric Mann Whitney U test when data were compared for individual patient characteristics. However, parametric t tests were used for comparisons before and after liraglutide mean 24-hour CGM glucose values, grouped for individual patients or for the entire CGM data sets.

Average glucose values for composite of each patient were used to estimate HgbA1C values before and after liraglutide using a conversion scale for relating glucose levels to HbA1c values [8].

Glucose variability was described in each patient before and after liraglutide.

a) Composite analysis of both pre-liraglutide and post-liraglutide Individual 24-hour study data was combined to provide composite analysis of these two sets of fifty-four 24-hour studies.

b) Composite 24-hour study data was divided into 8 equal 3-hour segments for calculation of segmental glucose variability as a tool to anticipate periods of hypoglycemic risk.

Results

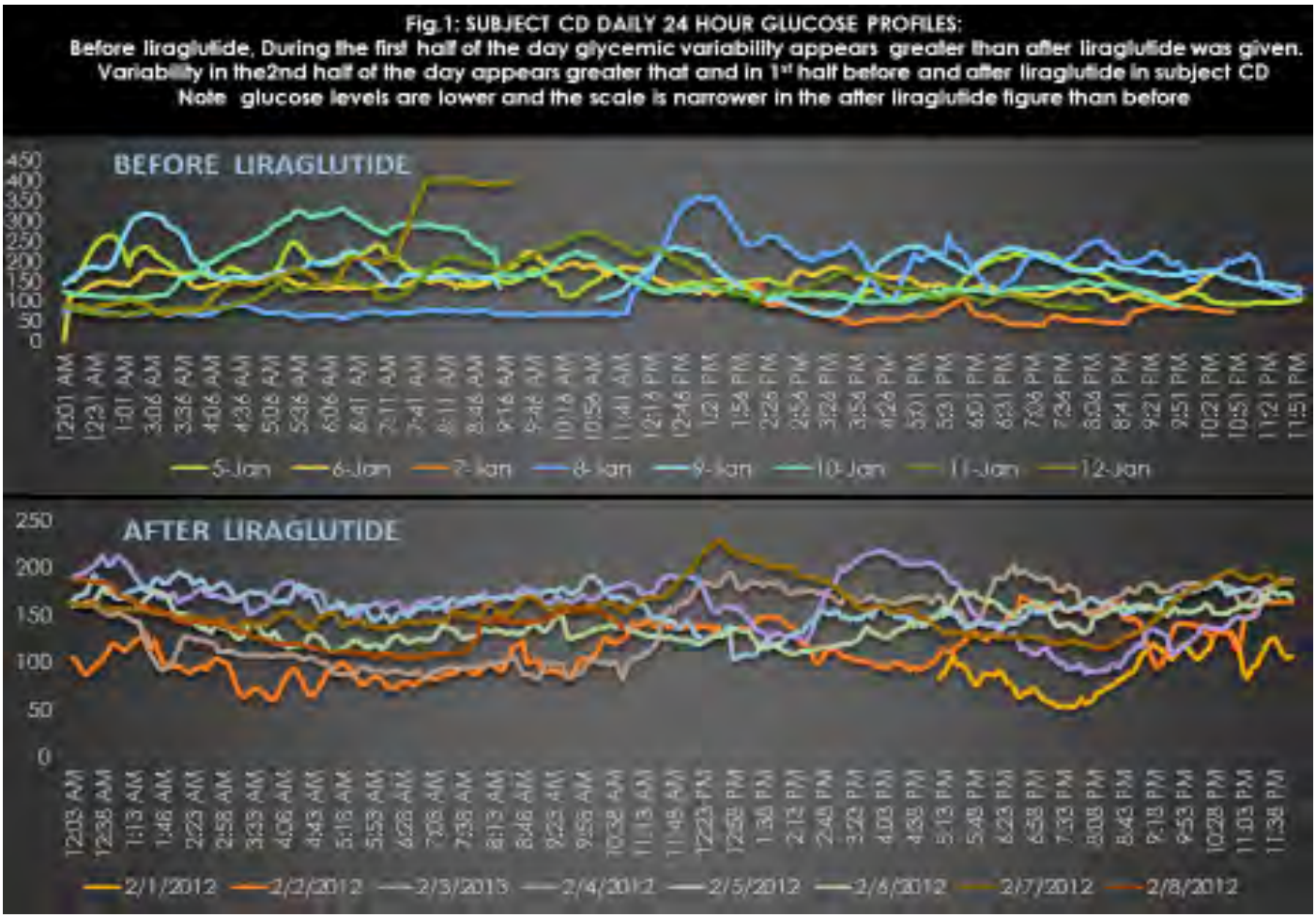
Self-monitoring of blood glucose (SMBG) was performed in five patients during the CGM studies before liraglutide to demonstrate the apparent difference between the data sets obtained from SMBG and CGM. SMBG data was absent during hours of sleep while CGM data was recorded every 5 minutes. (Data not shown). During wakefulness, SMBG data recording occurred only 3 times a day. Individual values for SMBG data fails to inform about glucose level direction or variability.

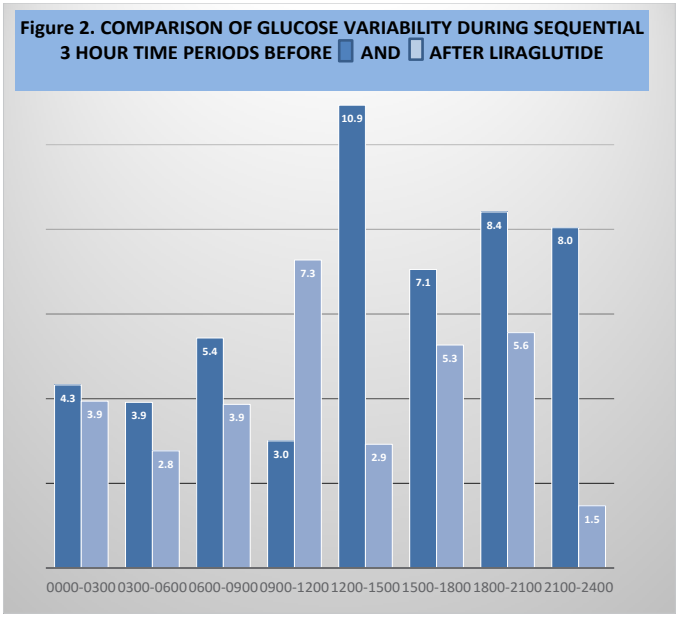
Figure 1 shows glycemic variability changing from day to day, and within different segments of the same day. After liraglutide, glucose levels are lower and the scale is narrower than before liraglutide, suggesting successful suppression of both variability and lower glucose levels in this subject. After liraglutide, confluent glucose trends are seen before midday in this subject in contrast to morning trend variability seen before liraglutide, but inter-day trend variability persisted during the 2nd half of the day both before and after liraglutide was given.

Comparing overall 24 hour CGM glucose trends we found the pre-liraglutide variability (S.D. =25.4) decreased by 24% after liraglutide (to S.D. =19.4) in the 10 patients studied. Mean glucose values decreased from 177 mg% before lira-

glutide to 154 mg% after liraglutide treatment; with calculated mean HbA1c decreased from 7.9% to 7.1%, all with p>.05.

Hypoglycemia susceptibility is not identified with CGM in all patients as shown, for example, in Figure 1. It is noteworthy that day-to-day variability in 24-hour glycemic profiles





Further, we asked if there was one part of the day when variability was decreased more than others so that 24-hour CGM repetition would not be needed. However, we found variability decreased in seven of the eight three hour time segments in our 24 hour data sets (Figure 2).

is a common event in our patient group. Regardless of the decrease in glycemic variability we calculated decreased glucose variability before and after liraglutide administration, looking for a metric of hypoglycemic vulnerability. However, the visual assessment from figure 1 suggests that this glucose variability measure does not enhance prediction of hypoglycemic vulnerability for individual patients. A hypoglycemic event could increase glucose variability, as seen here in figure 1, in the top panel, blue line. At 1140 am it depicts a rapid increase in glucose levels from a low to a high value after hypoglycemia persisted for several hours according to the CGM readings.

Discussion

Our data supports CGM, in preference to SMBG, in evaluating glycemic trends and their variability.

Liraglutide role in T2DM is well-described [9]. Efficacy and safety are based on HbA1c, target glucose levels without hypoglycemia, and decreased glycemic variability [5-7]. Due to individual differences in medication effects and the life style of our patients, we and others[6] support using CGM measurements to illustrate glycemic variability. For example, while liraglutide alone infrequently produces hypoglycemia, hypoglycemic episodes are more likely to occur when it is added to insulin, a sulfonylurea, metformin [1, 6, 7] or thia-

zolidinedione [12].

Previous studies demonstrate [6] efficacy using variability with CGM in patients treated with exenatide LAR [13]. Other trials evaluating liraglutide efficacy do not address interactions with other hypoglycemic agents [2, 3]. Our findings suggest that persistently erratic glucose trending makes it difficult to anticipate hypoglycemic vulnerability timing. Greater daily consistency in glucose trends than seen in this trial is needed for that to occur [14].

Limitations to this trial include the small sample size, the erratic performance of CGM is some subjects and the need to do statistical averaging based on last value carried forward in the subjects whose data qualified for this fix. The subjects used different combinations of diabetes medications for treatment that could influence the outcomes we report. We expect that larger groups of patients whose consistency of combination diabetes therapy within the group may provide more compelling information of a liraglutide influence of decreasing glycemic variability in T2DM patients.

In this paper, we describe how glycemic variability measures can be clinically accessible with CGM. This intervention series offers hints for follow up studies of glycemic variability effects of add-on or substituted agents in T2DM patients. These include a larger group of subjects, more consistency in timing of medication administration, sleep, meals and daily activity and looking at drug - drug interactions one at a time [15]. Further studies, which address limitations we describe in this trial, can establish the importance of GCM based assessments of drug-drug interactions when add-ons or substitutions occur to improve outcomes in T2DM patients.

Conclusions

- CGM before and after liraglutide, demonstrates reduced glucose variability during serial 24 studies.
- CGM appears superior to SMBG in evaluation variability, anticipated HbA1c trends and hypoglycemic vulnerability.
- Selected 3-hour time segments may provide useful insights into interactions between medications when add-ons or substitutions are used to improve clinical outcomes in T2D patients.
- Adequately powered and appropriately controlled randomized trials are needed to confirm that CGM adds value in showing clinically meaningful hypoglycemic agent interactions when add-ons or substitutions occur inT2DM patients.

Acknowledgements

Clerical assistance from: Katie Fyke and Lisa Plaxe: Statistical assistance from Bruce Stouch, PHD: Assistance from: Philadelphia College of Osteopathic Medicine.

Conflict of Interest

Regarding duality of interest during previous 12 months with a company whose products are directly related to the subject matter of this manuscript.

References

1. Standards of Medical Care for Diabetes. Diabetes Care 38 Supplement 1: S14-S87, 2015.
2. American Association of Clinical Endocrinologists/ American College of Endocrinology Comprehensive Diabetes Management Algorithm 2015 Endocr Pract. 2015, 21(14):438-447.
3. Bolen S. Systematic review: comparative effectiveness and safety of oral medications for type two diabetes mellitus. Ann Intern Med.2007, 147(6): 386-399.
4. Cefalu WT, Buse JB, Del Prato S, Home PD, LeRoith D et al. Beyond Metformin: Safety Considerations in the Decision-Making Process for Selecting a Second Medication for Type two Diabetes Management. reflections from a diabetes care editors' expert forum. Diabetes Care, 2014. 37(9): 2647–2659.
5. Connell PJ, Thompson CK. Flexibility of Single-subject Experimental Designs. Part III: Using Flexibility to Design or Modify Experiments. J Speech Hear Disord. 1986, 51(3):214-225.
6. Moran DJ, Tai W. Reducing Biases in Clinical Judgment with Single-Subject Treatment Design. The Behavior Analyst Today. 2001, 2(3):196–206.
7. Package insert Victoza (liraglutide DNA origin) injection, Version: four, Novo Nordisk Plainsboro, NJ; Liraglutide for the treatment of type 2 diabetes mellitus. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010:46.
8. Sacks D. Correlation between HbA1c and Average Blood Glucose: Can HbA1c Be Reported as Estimated Blood Glucose Concentration? J Diabetes Sci Technol, 2007, 1(6): 801–803.
9. Hirsch IB. Glycemic Variability: It's not just about A1C Anymore! Diabetes Technology & Therapeutics. 2005, 7(5):780-783.
10. Monnier L, Colette C, Owens D. Glycemic Variability: The Third Component of the Dysglycemia in Diabetes. Is It Important? How to Measure It? J Diabetes Sci Technol. 2008, 2(6): 1094–1100.
11. Rodbard D. Interpretation of continuous glucose monitoring data: glycemic variability and quality of

glycemic control. Diabetes Technol Ther. 2009,11(S1):5-55.

12. Buse JB, Sesti G, Schmidt WE, et al. Liraglutide Effect Action in Diabetes-6 Study Group. Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. Diabetes Care. 2010, 33(6):1300–1303.

13. Kyriacou A, Ahmed A. Exenatide Use in the Management of Type 2 Diabetes Mellitus. Pharmaceuticals. 2010, 3(8): 2554–2567.

14. Pappada SM, Cameron BD, Rosman PM. Development of a Neural Network for Prediction of Glucose Concentration in Type 1 Diabetes Patients. J Diabetes Sci Technol. 2008, 2(5): 792–801.

15. Pappada SM, Cameron BD, Rosman PM, Bourey RE, Papadimos TJ et al. Neural network-based real-time prediction of glucose in patients with insulin-dependent diabetes. Diabetes Technology & Therapeutics. 2011,13(2):135-141.