

Hypoglycemia associated with off-label sitagliptin use

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Purpose: To describe a case of hypoglycemia induced by off-label use of sitagliptin in an adult patient with type 2 diabetes.

Case summary: Addition of sitagliptin to metformin, glimepiride, and NovoLog[®] 70/30 Mix induced hypoglycemia in a 55-year-old Caucasian female. Hypoglycemia improved, although still occurred periodically, following sulfonylurea discontinuation and a 28% insulin dose reduction. Hypoglycemic symptoms were absent during a 3-day dechallenge but occurred again upon sitagliptin reinitiation.

Discussion: Although the mechanism of action of sitagliptin does not predispose patients to hypoglycemic events, when combined with hypoglycemia-inducing medications, eg, sulfonylureas or insulin, and possibly meglitinides, the incidence likely increases.

Conclusions: Caution should be used when combining sitagliptin with either sulfonylureas or insulin, and possibly meglitinides, for the treatment of type 2 diabetes as hypoglycemia may ensue. Hypoglycemia due to off-label combinations with insulin and sitagliptin may be prevented by reducing meal-time insulin doses. Prescribers and patients should vigilantly monitor for hypoglycemic events when using sitagliptin off-label with similar pharmacologic combinations such as meglitinides and other rapid-acting insulin products. Additionally, clinicians may encounter resistance from insurance companies to cover such off-label combinations.

Keywords: diabetes, DPP-IV inhibitor, sitagliptin, hypoglycemia, drug-induced, off-label

Introduction

Sitagliptin is an incretin enhancer and the first marketed medication belonging to the gliptin class. FDA-approved indications include adjunct therapy to diet and exercise in adult patients with type 2 diabetes mellitus (DM).¹ Sitagliptin has also been studied in combination with metformin, thiazolidinediones, and sulfonylureas; however, sitagliptin “has not been studied in combination with insulin”.¹ In fact, no published literature exists regarding incidence or severity of hypoglycemia when sitagliptin is used off-label in combined with insulin therapy. This case describes the onset and severity of hypoglycemia induced upon initiation of sitagliptin to insulin therapy. The authors recommend methods to avoid hypoglycemia when using this off-label combination.

Patient case

A 55-year-old Caucasian woman was diagnosed with type 2 DM 15 years prior to presentation. Her DM remained uncontrolled with fasting blood glucose (BG) values ranging between 300 mg/dl and 400 mg/dl, and as high as 500 mg/dl in the recent past as measured by her Ascensia[®] Contour[®] which reports plasma values. Her most recent hemoglobin A1C (A1C) was 8.0% and previously was 8.4%. Antidiabetic medications included metformin 500 mg TID, glimepiride 4 mg BID, and NovoLog[®] 70/30 Mix FlexPen 50 units BID. The patient reported adherence to all drug therapies, no previous hypoglycemic symptoms or episodes, and received diet counseling at most appointments. Other medical conditions and medications included the following: obesity (body mass index [BMI] 40.3, 110 kg)

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treated with diet and exercise, insomnia treated with zolpidem 10 mg qHS prn, depression treated with bupropion XL 300 mg daily and alprazolam 0.5 mg TID, hypertension treated with valsartan/hydrochlorothiazide 160/25 mg daily, dyslipidemia treated with rosuvastatin 10 mg daily, and heartburn treated with lansoprazole 30 mg daily.

Due to continued elevated BG values, sitagliptin was added to her current therapy; no other medication alterations were made at this time. As the patient's creatinine clearance (CrCl) was normal (serum creatinine [SCr] 0.7 to 0.8 mg/dl) sitagliptin was dosed at 100 mg daily, which she administered at 6 AM. At the patient's visit, 10 days later, she reported fasting, lunch-time, and afternoon BG values of 200 mg/dl, 100 mg/dl, and 200 mg/dl, respectively. She was particularly concerned about several low values around 50 mg/dl that consistently occurred at 10 AM with symptoms of diaphoresis, tachycardia, and ataxia. In response, glimepiride was discontinued, and her insulin was slowly self-titrated downward to 36 units BID. All other medications and doses were maintained. Two months following sitagliptin initiation her A1C had decreased to 6.7% and her morning BG values ranged between 108 and 130 mg/dl while evening values were always less than 170 mg/dl. Periodically BG levels nadired in the upper 60s mg/dl with minimal hypoglycemic symptoms.

Approximately one year after sitagliptin initiation, the patient's Medicare Part D plan required a prior authorization (PA). The patient was unable to pay full price for sitagliptin and was without the medication for three days. During this time all other medication doses remained the same and she experienced no symptoms of hypoglycemia or documented BG less than 70 mg/dl. While the insurance provider was contacted the patient was provided with samples of sitagliptin and again mild hypoglycemic events immediately presented.

The PA was submitted with proof of efficacy (decline in A1C) and other medications previously and currently used. The PA was promptly rejected and an appeal was denied. During a follow-up phone conversation, a representative from the Medicare Part D provider explained sitagliptin would continue to be rejected because of the off-label combination with insulin regardless of the patient's disease state improvements. The clinician plans to provide the patient with sitagliptin samples until she is able to switch Medicare Part D plans in hopes of regaining sitagliptin coverage.

Discussion

Sitagliptin enhances the incretin system by inhibiting the dipeptidyl peptidase-IV (DPP-IV) enzyme.¹ DPP-IV is responsible for the degradation of incretin hormones,

glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).² GLP-1 is released from L cells within the terminal ileum and colon following ingestion of carbohydrate-rich foods, while GIP is secreted from duodenal K cells following fat consumption.² The rapid metabolism by DPP-IV results in the incretins' very short half-lives³ of less than 2^{2,4-6} and 7 minutes,² respectively. By inhibiting the DPP-IV enzyme, sitagliptin increases the duration of action of incretin hormones.³

Incretin hormones stimulate pancreatic β -cells to release insulin^{4,7} in a glucose-dependent fashion.⁸ Additionally, by affecting insulin production, incretins also indirectly decrease unnecessary hepatic glucose production by inhibiting glucagon secretion from pancreatic α -cells.⁸ Based on these mechanisms of action, incretins do not intrinsically cause hypoglycemia; therefore, prolongation of endogenous incretins' duration of action is unlikely to induce hypoglycemia alone.

Indeed, sitagliptin monotherapy studies revealed low hypoglycemic rates (1.3% vs 0.8%)⁹ that were not statistically significant from placebo.^{3,10} Other trials assessing the efficacy and safety of sitagliptin combined with metformin¹¹ or thiazolidinedione¹² treatments in adult patients diagnosed with type 2 DM found similar rates of hypoglycemia between treatment arms as well. As noted in the prescribing information, when sitagliptin is combined with metformin or thiazolidinedione treatment, a minimal background prevalence of hypoglycemia is expected and no increase in hypoglycemia is observed.¹ Collectively, sitagliptin trials note placebo-adjusted hypoglycemic events ranging from 1.0% to 1.5%.¹³ Adverse reactions of hypoglycemia were based upon all patient reports of hypoglycemia and did not require concurrent glucose measurements.¹ Evaluation of these studies proves that sitagliptin does not induce hypoglycemia alone nor when added to oral hypoglycemic medications known to not cause hypoglycemia. Conversely, when sitagliptin is added to sulfonylurea therapy an increase in hypoglycemia is noted to occur in 12.2% vs 1.8% ($p < 0.001$) of subjects.¹⁴ Because combining sitagliptin with a sulfonylurea substantially increases the risk of hypoglycemia one may anticipate a similar increased risk when adding sitagliptin to insulin.

Analyzing the time course between sitagliptin administration and onset of hypoglycemia in the patient case further highlights the likelihood of this drug combination induced adverse event. Following sitagliptin initiation, the patient experienced hypoglycemic events consistently occurring 4 hours post dose. Pharmacokinetic sitagliptin studies have found the median time to maximum concentration (T_{max}) to

range from 2 to 4 hours following doses of 200 mg and 25 mg, respectively.^{13,15} Therefore, the maximal inhibition of DPP-VI and therefore the maximal increase activity of incretins would occur at this T_{max} , which in turn would lower blood glucose at this time and potentially result in hypoglycemia. The T_{max} of sitagliptin and the temporal relationship between sitagliptin administration and hypoglycemic onset further increases the plausibility of sitagliptin-induced hypoglycemic events when taken in combination with insulin therapy.

Resolutions of hypoglycemic symptoms upon sitagliptin dechallenge, and reappearance upon reinitiation, additionally highlight the likelihood of this drug combination induced adverse event. In fact the half-life of sitagliptin is 12.4 hours;¹ therefore, approximately 25% of the dose would remain 24 hours post dose which would result in minimal clinical activity.⁸ One would therefore expect glycemic changes due to sitagliptin to no longer be present several days following therapy discontinuation. Likewise, adverse events, such as hypoglycemia would also quickly resolve, as seen in the patient case upon dechallenge.

Per the package insert, “when Januvia is used in combination with a sulfonylurea, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia”;¹ however, an exact dose reduction is not known nor recommended. Once the patient discontinued her maximally-dosed sulfonylurea and decreased her insulin therapy by 28%, only mild hypoglycemic signs remained. In light of this patient case empiric reductions of sulfonylurea or pre-meal insulin doses by 30% to 50% at the initiation of sitagliptin therapy seems prudent. Re-titration of doses may be necessary as diabetes is a progressive disease. Patients should also be educated regarding the signs and symptoms of hypoglycemia, as well as methods to correct low blood sugars.

Conclusion

The risk of hypoglycemia induced by sitagliptin when used as monotherapy or combined with metformin or a thiazolidinedione is similar to that of placebo, but increases when combined with a sulfonylurea. The incidence also appears to increase when sitagliptin is added to insulin therapy. Practitioners should be advised to monitor patients closely for hypoglycemia when using such a combination with sitagliptin. It would be prudent to prophylactically reduce the meal-time insulin doses when initiating sitagliptin to

help avoid hypoglycemic events, and to educate patients on the signs, symptoms, and treatment of hypoglycemia. Lastly, clinicians may encounter obstacles with insurance providers when prescribing sitagliptin off-label especially in combination with insulin.

Disclosure

The authors report no conflicts of interest in this work.

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