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Case Report

Severe Hypoglycemia in a Patient With Type 1 Diabetes Mellitus Recently Started on Sacubitril/Valsartan: A Case Report

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ABSTRACT

This report describes an episode of severe hypoglycemia in a 55-year-old woman with type 1 diabetes mellitus approximately 2 weeks after initiating sacubitril/valsartan for heart failure. She was receiving a continuous subcutaneous insulin infusion and denied any severe hypoglycemic events in the prior 13 years. She experienced a second hypoglycemic episode 1 week later. She subsequently reduced her insulin dose and continued on sacubitril/valsartan. Eight months later, she did not have any recurrent hypoglycemic episodes. Clinicians should be aware of this potential adverse effect and educate patients on concomitant insulin therapy to monitor for symptoms of hypoglycemia when initiating sacubitril/valsartan.

RÉSUMÉ

Les auteurs présentent le cas d'une femme de 55 ans atteinte de diabète de type 1 qui a subi un épisode d'hypoglycémie sévère environ deux semaines après la mise en route d'un traitement de l'insuffisance cardiaque par l'association sacubitril-valsartan. La patiente recevait alors de l'insuline par perfusion sous-cutanée continue et avait affirmé n'avoir subi aucun épisode d'hypoglycémie sévère depuis 13 ans. Un deuxième épisode d'hypoglycémie est survenu une semaine après le premier. La patiente a par la suite réduit sa dose d'insuline et poursuivi le traitement par l'association sacubitril-valsartan. Huit mois plus tard, elle n'avait subi aucun autre épisode d'hypoglycémie. Il importe que les cliniciens soient au fait de cet effet indésirable possible et qu'ils avisent leurs patients sous insulinothérapie concomitante de surveiller les symptômes d'hypoglycémie à la mise en route d'un traitement par l'association sacubitril-valsartan.

Sacubitril/valsartan is a novel angiotensin receptor-neprilysin inhibitor indicated in the management of patients with heart failure with reduced ejection (HFrEF).[1] This article reports a case of severe hypoglycemia that was associated with the initiation of sacubitril/valsartan.

Case Report

A 55-year-old woman (57 kg) under the care of a specialized heart failure clinic was initiated on sacubitril/valsartan for HFrEF. The patient provided written informed consent for this case report. Her medical history included HFrEF (secondary to myocardial ischemia), coronary artery disease (myocardial infarction and coronary artery bypass graft surgery in 2006), type 1 diabetes mellitus, dyslipidemia, and hypothyroidism. An echocardiogram before initiating sacubitril/valsartan demonstrated a left ventricular ejection fraction of 30% to 35% with severe mitral valve regurgitation, and her functional status was New York Heart Association class II. Her medications included candesartan 32 mg daily, carvedilol 12.5 mg twice daily, acetylsalicylic acid 81 mg daily, atorvastatin 40 mg daily, levothyroxine 75 μg daily, and furosemide 20 mg daily as needed. Additionally, she took omega-3 fatty acids, glucosamine/chondroitin, and vitamin D daily. She was previously taking spironolactone, but it was discontinued secondary to hyperkalemia. Her diabetes mellitus was managed by insulin lispro, which she received via a continuous subcutaneous infusion pump at 22 to 24 units daily (0.39-0.42 units/kg/d) divided approximately as 50% basal and 50% bolus based on her serum blood glucose. She reported her daily blood glucose readings were stable. She had been using an insulin pump for 13 years. She denied any hypoglycemic episodes requiring medical assistance since starting on the insulin pump. Seven weeks before initiating sacubitril/valsartan, her glycosylated hemoglobin (A1c) was 6.6%.

Her candesartan was discontinued, and she was initiated on sacubitril/valsartan 49/51 mg twice daily. After 2 days, the

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Ethics Statement: This case report adheres with the University of British Columbia Clinical Research Ethics General Guidance Notes (article 4.4.2). Individual case reports do not meet the definition of research, as they are considered to be a medical/educational activity. The patient provided written informed consent for this case report.

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See page 178 for disclosure information.

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Novel Teaching Points

- Sacubitril/valsartan, a novel angiotensin receptor-neprilysin inhibitor indicated in the management of heart failure with reduced ejection fraction, has limited postmarket safety data.
- Sacubitril/valsartan was associated with a lower mean glycosylated hemoglobin, compared with enalapril, in the PARADIGM-HF trial.
- Case reports have demonstrated an association between hypoglycemia and initiation of sacubitril/valsartan.
- Clinicians should be aware of the potential risk of hypoglycemia when initiating sacubitril/valsartan in patients on insulin therapy, particularly patients receiving a continuous subcutaneous insulin infusion.

dose was reduced to 24/26 mg twice daily secondary to symptomatic hypotension (home blood pressure of 95/50 mm Hg). Sixteen days later, she presented to an emergency department with severe hypoglycemia. While grocery shopping, she began to feel symptoms of hypoglycemia. She collapsed on her way to her vehicle and was found unresponsive by store staff. Emergency medical services were contacted, and chest compressions were initiated. When emergency medical services arrived, she was determined to be breathing with a palpable pulse, so chest compressions were discontinued. Her blood pressure was 138/78 mm Hg with a heart rate of 78 beats/min. Her serum blood glucose was 1.2 mmol/L. She was given a dose of dextrose 10% intravenously, and her level of consciousness improved. She was transported to the hospital. At triage, her Glasgow Coma Scale was 15/15, blood pressure was 138/78 mm Hg, heart rate was 48 beats/min, respiratory rate was 18 breaths/min, oxygen saturation was 99% on room air, and serum blood glucose was 8.0 mmol/L. Her additional blood work was noncontributory. Electrocardiography revealed sinus bradycardia with a heart rate of 57 beats/min. She denied any recent adjustments to her insulin dose. She did not report any variation to her dietary intake on the day of the event. Her dietary pattern, physical activity, and weight were essentially unchanged in the months leading up to the event. After approximately 2 hours, she departed the emergency department of her own volition. Approximately 1 week later, she experienced a second episode of hypoglycemia. A family member treated her with 1 mg of glucagon intramuscularly, and her hypoglycemia resolved. She did not seek medical attention. Subsequently, she reduced her basal dose of insulin lispro from approximately 10 units to 9 units daily. She continued on sacubitril/valsartan at 24/26 mg twice daily. Six weeks after starting sacubitril/valsartan, her A1c was 6.8%. Eleven weeks after starting sacubitril/valsartan, her dose was increased to 24/26 mg in the morning and 49/51 mg in the evening with no evidence of adverse effects. Eight months after her initial hypoglycemic episode, she continued on sacubitril/valsartan and denied any further episodes of hypoglycemia that required medical intervention or attention.

Causality was assessed using the Naranjo algorithm for adverse drug reactions.[2] Four points (of 13) were assigned because the adverse event appeared after the suspected drug was administered, the adverse event was confirmed by objective evidence (serum blood glucose of 1.2 mmol/L), and other cases of hypoglycemia associated with sacubitril/valsartan have been reported.[3] Therefore, it was classified as a possible adverse drug therapy event. The adverse reaction was reported to the Canada Vigilance Program.[4]

Discussion

This case report describes 2 episodes of severe hypoglycemia in a patient with well-controlled type 1 diabetes mellitus who had recently started sacubitril/valsartan. This adverse event was possibly related to her sacubitril/valsartan, as per the Naranjo algorithm, which is a 10-item questionnaire to help determine the probability that an adverse event was related to a drug.[2] Probability is determined to be doubtful, possible, probable, or definite using factors such as timing of the reaction, whether the reaction resolved with drug discontinuation, and whether the reaction recurred with readministration. However, the Naranjo algorithm does not take into consideration additional patient factors, such as her lack of hypoglycemic episodes in the prior 13 years, and compensatory reduction in her insulin dose that preempted discontinuation of her sacubitril/valsartan. Notwithstanding, it is possible her episode of hypoglycemia occurred coincidentally after initiating sacubitril/valsartan, although another clear potential cause could not be identified.

Sacubitril/valsartan is a first-in-class pharmacotherapeutic agent with relatively limited postmarket data. It was approved by Health Canada in November 2015 for the treatment of HFrEF in patients with New York Heart Association class II or III symptoms to reduce the incidence of cardiovascular death and heart failure hospitalization.[1] The Canadian monograph currently does not list hypoglycemia as a potential adverse effect of sacubitril/valsartan, nor is hypoglycemia listed as a postmarket adverse drug reaction.[1] Sacubitril/valsartan was approved on the basis of the results of the **P**rospective Comparison of **ARNI** With **A**CEI to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure (PARADIGM-HF) trial, which demonstrated that sacubitril/valsartan reduced cardiovascular deaths and heart failure hospitalizations compared with enalapril in patients with HFrEF.[5] Forty-five percent of patients (3778/8399) in the PARADIGM-HF trial had diabetes mellitus or an A1c of $\geq$ 6.5%.[6] However, only 0.7% of patients (57/8399) had type 1 diabetes mellitus (personal communication with Dr John McMurray on January 14, 2020). Hypoglycemia was not reported as a common adverse effect in the PARADIGM-HF trial.[5]

There are data to support that sacubitril/valsartan is associated with lower serum blood glucose. A post hoc subgroup analysis of the 3778 patients with diabetes mellitus or an A1c of $\geq$ 6.5% in the PARADIGM-HF trial demonstrated improved glycemic control with sacubitril/valsartan.[6] Mean baseline A1c was similar between groups (7.48% in the sacubitril/valsartan group and 7.41% in the enalapril group). Over 3 years of follow-up, patients in the sacubitril/valsartan group had a lower mean A1c compared with patients in the enalapril group (mean between-group difference of -0.14%, $P = 0.006$). Although this difference was statistically significant, it is questionable whether it would be clinically meaningful. As well, fewer patients in the sacubitril/valsartan group initiated new insulin therapy over the study follow-up period

(7% in the sacubitril/valsartan group vs 10% in the enalapril group, $P = 0.005$), although incident diabetes mellitus was not significantly different between groups. There were more patients in the sacubitril/valsartan group who experienced a hypoglycemic event (53 events in the sacubitril/valsartan group vs 44 events in the enalapril group), but the difference was not statistically significant (hazard ratio, 1.18; 95% confidence interval, 0.79-1.76; $P = 0.42$). The authors hypothesized that the lower A1c observed with sacubitril/valsartan could be secondary to increased circulating levels of natriuretic peptides and bradykinin, which are involved in insulin sensitivity and metabolism. Furthermore, neprilysin, which is inhibited by sacubitril, is involved in the breakdown of glucagon-like peptide 1. The authors also highlighted previous research that showed omapatrilat, a combined angiotensin-converting enzyme and neprilysin inhibitor, induced insulin sensitization in Zucker fatty rats.[7] Notwithstanding, these data should be considered hypothesis generating, because this was a post hoc subgroup analysis.

A search of MEDLINE, PubMed, and Embase (inception to January 2020) using the terms "sacubitril/valsartan" and "diabetes mellitus" identified 1 case report of a patient who required a reduction in his insulin dose after starting sacubitril/valsartan. The report described a 62-year-old man who was being treated with a continuous subcutaneous insulin infusion for type 2 diabetes mellitus and was initiated on sacubitril/valsartan for the treatment of HFrEF.[3] An analysis of his insulin pump demonstrated a 22% relative reduction in his daily insulin requirement because of frequent postprandial hypoglycemic events. After 4 months of therapy, his A1c had decreased by 0.4% (6% relative reduction), and his mean serum blood glucose was 1.1 mmol/L lower (14% relative reduction) from 1 to 4 months after starting sacubitril/valsartan.

A search of the Canada Vigilance Adverse Drug Reaction Online Database from January 1, 1965, to September 30, 2019, using the terms "Entresto" and "hypoglycaemia," revealed 9 cases of reported hypoglycemia with sacubitril/valsartan (including the present case).[4] However, it is not known how many (if any) of the patients had type 1 diabetes mellitus, and most of the reports listed multiple adverse reactions. Only 1 patient was reported as taking concomitant insulin (glargine). Of note, the *Protecting Canadians from Unsafe Drugs Act* (also known as "Vanessa's Law") now requires mandatory adverse drug reaction reporting by healthcare institutions.[8]

Conclusion

This case provides further evidence that sacubitril/valsartan may increase the risk of hypoglycemia in patients receiving insulin via a continuous subcutaneous infusion, particularly patients with type 1 diabetes mellitus. Clinicians should be aware of this potential adverse effect and educate patients who are on concomitant insulin therapy who are initiating sacubitril/valsartan to monitor for symptoms of hypoglycemia or, if warranted, empirically reduce the patient's insulin dose.

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Disclosures

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