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Case Report

Sevelamer HCl-Induced Spontaneous Hypoglycemia: A Case Series

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Abstract

Drug-induced hypoglycemia is a common adverse drug reaction (ADR) that occurs frequently among the hospitalized patients. Sevelamer hydrochloride (HCl) is considered as a safe drug in the context of ADR. It works locally with no significant systemic exposure. In two separate cases of this case series, sevelamer HCl caused spontaneous hypoglycemia. The patient in case 1 had sound renal function whereas case 2 patient was suffering from chronic kidney disease and he was on maintenance haemodialysis. Hyperphosphataemia was found in both the patients and sevelamer HCl was intended for treating Hyperphosphataemia. The patients (case 1 and 2) had no previous experience with sevelamer. After administering couple of oral dosages of sevelamer, both the patients developed hypoglycemia (lowest blood glucose level found in case 1 patient: 4.7 mmol/L and case 2 patient: 3.9 mmol/L), spontaneously. Sevelamer was suspected as the culprit drug for that ADR and stopped. After discontinuation of the sevelamer, no further hypoglycemia incidence was found in those patients.

Keywords: *Sevelamer Hydrochloride; Hyperphosphataemia; Hypoglycemia*

Introduction

Drug-induced hypoglycemia (DIH) is a frequent event found in the hospital admitted patients with a common difficulty to detect at the early event stage. Study found that 23% of the hospitalized patients developed DIH attributed to adverse drug event (ADE). Other than insulin and sulfonylureas in diabetic patients, different known or unknown drugs are also responsible for developing such unwanted event even in the non-diabetic patients [1].

Hyperphosphataemia is a common complication in patients with chronic kidney disease (CKD) and inadequate phosphorus control-associated high rate of mortality and morbidity is a serious concern in the end stage (stage 5) of CKD patients [2]. Sevelamer, in the partial hydrochloride (HCl) salt form or carbonated form, is an oral phosphate-binding agent used in the management of hyperphosphataemia in chronic kidney disease (CKD) [3]. The Food and Drug Administration (FDA) of United States (US) recommended the use of sevelamer in the treatment of hyperphosphataemia in adult patients on haemodialysis with CKD stage 4 and 5 [4]. Sevelamer-induced hypoglycemia is a very rare and life-threatening ADE specially, during haemodialysis. In this case series of two cases in two different time period, sevelamer HCl-induced acute hypoglycemia event was found.

Case Report

Case 1

A 52-year old male patient was admitted in the intensive care unit (ICU) with the history of acute respiratory distress syndrome (ARDS) for the last 2 days and low blood pressure. His recorded SpO_2 was 83% in room air and immediately after admitting in the ICU, he was supported by 4 liter external oxygen supply. At his admission day, his body temperature was 101.3°F, blood pressure was 100 over 65,

pulse rate was 105 beats/minute, heart rate was 109 beats/minute, respiration rate was 26 breaths/minute, serum creatinine level was 0.9 mg/dL, urea was 69 mg/dL, Serum albumin was 2.7 mg/dL and TCO_2 was 25. His random blood glucose was 8.4 mmol/L and average daily blood glucose level was 8.3 mmol/L. He did not get any insulin or oral antidiabetic drugs. His white blood cell (WBC) count was 14,000 per µL of blood. His serum phosphorus level was 6.2 mg/dL (considered as hyperphosphataemia). Other serum electrolyte levels were found normal. His Glasgow coma score (GCS) was E (4), V (3) and M (5).

To treat his hyperphosphataemia, he was prescribed with tablet sevelamer HCl 400 mg, twice daily, orally. Before that time, he was not ever experienced with sevelamer. After 2 hours of the third dose of sevelamer administration, his blood glucose level was measured under the ICU's routine blood glucose monitoring protocol and found 4.7 mmol/L (recorded as lowest level), and similar type of low blood glucose level was recorded in following multiple readings. At that time, patient was on normal daily diet and no diet change was done by that time. Sevelamer was suspected for that ADR on the basis of the only new included drug therapy and stopped immediately. Blood glucose level measured after 4 hours of sevelamer discontinuation was normal (7.9 mmol/L).

Case 2

A 77-year old male patient with CKD was admitted in our nephrology unit with the history of pneumonia. His recorded SpO_2 was 89% in room air and initially was supported by 2 liter oxygen. His blood pressure was 130 over 95, pulse rate was 102 beats/minute, heart rate was 109 beats/minute, respiration rate was 23 breaths/minute He was on maintenance haemodialysis. His creatinine base-line level was 2 mg/dL. He was a patient with diabetes mellitus and his recorded random blood glucose level was 10.4 mmol/L. For his diabetes, he was existed on daily subcutaneous insulin therapy: insulin as part (rapid-acting insulin) 12 units/day in divided doses and insulin glargine (long-acting insulin) 6 units/day once daily. According to his home-based daily blood glucose monitoring log, the average daily blood glucose level was 9.2 mmol/L. At that day, he was found with mild pneumonia with normal blood pressure and full consciousness. His WBC count was 12,000 per µL of blood, low grade fever (101°F) and normal hepatic functions. His urine output was 40 mL/hour. His serum electrolyte levels were normal but, serum phosphorus level was suddenly raised to 7.1 mg/dL (considered as hyperphosphataemia).

To manage his hyperphosphataemia, he was administered with tablet sevelamer HCl 400 mg (twice daily) orally. He had no previous history of taking sevelamer for hyperphosphataemia management. After 3 hours of administering the second dose of sevelamer, he developed hypoglycemia (3.9 mmol/L was the lowest level). After that, in the next 2 random blood glucose reading, similar type of blood glucose level was observed, spontaneously. At that time, patient was on normal daily diet and no diet change was done by that time. Sevelamer was the only drug suspected for that ADE on the basis of the only new included drug therapy and discontinued finally. No further hypoglycemic event was noticed after stopping sevelamer therapy.

Discussion

In both the cases, a close common relationship between Sevelamer HCl and acute, spontaneous hypoglycemia among the patients was observed. Sevelamer HCl is a calcium and metal-free hydrophilic drug having a non-absorbable amine-based polymer. After administering in solid dosage form through oral route, the highly protonated form of this drug basically interacts with the negatively charged phosphate ions in the gastrointestinal (GI) tract as a result of van der Waals interaction (electrostatic interaction) and hydrogen bonding [5]. Ultimately, the plasma concentration of phosphate is reduced as a result of decreased absorption from the GI tract and increased faecal excretion of phosphate [3]. Sevelamer works locally in the GI tract and does not have any systemic exposure. As a result, the possibility of sevelamer-induced systemic ADR, renal impairment and hepatic impairment is very negligible [3,5]. A recent study found that sevelamer has bile-binding ability that reduce the GI absorption of fat soluble vitamins (A, D, E, K) and cholesterol [6]. Furthermore, sevelamer HCl binds with bacterial lipopolysaccharide and reduce bacterial endotoxins as well as pro-inflammatory precursors in the host blood through inhibiting advanced glycation end-products (AGEs) in the intestine, demonstrating its anti-inflammatory potentiality [3,7].

DIH among the hospitalized patients is a common incidence and sometimes overlooked, unintentionally by the healthcare professionals leading to an unwanted therapeutic-threats to the patients [1]. Study found that only because of drug-induced hypoglycemia, hospital staying time was extended to 4 days and related mortality rates raised to 1.3% [8]. A systemic review found a list of different drugs

responsible for developing hypoglycemia and most of the incidences were happened at regular dosages [3]. In our cases, patients received sevelamer at regular dosages and developed hypoglycemia significantly with normal daily diet. In a randomized, open-label, crossover study by Vlassare., *et al.* found that sevelamer reduces the significant mean value of HbA1c (-0.67%) [4]. Basically, sevelamer is approved by FDA for the treatment of hyperphosphataemia in patients with CKD and end-stage renal disease (ESRD) at predialysis stage. Some recent preclinical and clinical trial reports showed the blood glucose and lipid-lowering effects of sevelamer in type-2 diabetic patients and suggested the new potential role of sevelamer in diabetes treatment. The actual mechanism of glucose-lowering effect of sevelamer was not still clearly understood but, it has been suggested that analogous biophysical and different biochemical properties of sevelamer including the increased release of the incretin hormone GLP-1, may be the potential factors [3].

It is strongly believed that the potential role of sevelamer as a blood glucose-lowering agent is based on the sequestration of bile acids which deliver sequestrated bile acids to the L cell-rich colon causing endogenous GLP-1 secretion, extensively. After releasing from L cells, with a short half-life (~1.5 minutes), GLP-1 is degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), locally. Increased level of GLP-1 secretion may stimulate afferent vagal sensory nerve fibers locally in the intestinal mucosa and liver. This phenomenon triggers the activity of hypothalamus and finally pancreas becomes over functional. As a result, in response to the excess level of secreted insulin in the blood, glucose level is reduced drastically leading to hypoglycemia [9]. The above mentioned HbA1c lowering effect of sevelamer without affecting the fasting plasma glucose level (-1.96mmol/l) indicates the ability of sevelamer to alter the glycemic control through reducing the postprandial blood glucose level [3,4,9]. A similar type of secondary response of sevelamer may be accountable to develop spontaneous hypoglycemia in our case patients, where one patient (case 2) had CKD and another patient (case 1) had a sound renal function.

Conclusion

Drug-induced hypoglycemia is a frequently occurring event in the hospitalized patients and different known and unknown drugs are responsible for that unpleasant ADR. Sevelamer is considered as a safe drug due to its localized activities in the gut. In the two separate cases of this case series, sevelamer HCl-induced spontaneous hypoglycemia event was found which is really very rare.

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Conflict of Interest

There is no conflict of interest to declare.

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