

Recurrent Hypoglycemia in a Hemodialysis Patient Related to Propoxyphene Treatment

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There are various etiologies for hypoglycemia in patients with chronic renal failure, and its pathogenesis is complex. Concomitant use of medications is the most common cause. We report a rare case of an 82-year-old woman with type 2 diabetes mellitus in end-stage renal disease undergoing maintenance hemodialysis, who experienced recurrent symptomatic hypoglycemia during treatment with propoxyphene for pain relief. Hypoglycemia occurred simultaneously with elevated levels of serum immunoreactive insulin and C-peptide. After discontinuing propoxyphene, hypoglycemia mitigated and the level of insulin returned to normal range. Our case reminds us that propoxyphene-induced hypoglycemia should not be ignored, especially in hemodialysis patients with cold sweats, agitation and depressed consciousness. [*J Chin Med Assoc* 2007;70(7):286–288]

Key Words: hemodialysis, hypoglycemia, propoxyphene

Introduction

Glucose homeostasis and insulin metabolism are complex in patients with chronic renal failure. Though most uremic patients are insulin-resistant with associated glucose intolerance, hypoglycemia occurs in some patients undergoing hemodialysis. Both impaired insulin degradation and reduced renal gluconeogenesis in uremic patients increase the risk of hypoglycemia.^{1,2} Drug-induced hypoglycemia is common in uremic patients. But other factors, including sepsis, alcohol consumption, concomitant liver disease, congestive heart failure and malnutrition, possibly trigger the occurrence of hypoglycemia.

Propoxyphene is an opioid analgesic chemically similar to methadone, which is used for analgesia. We describe a patient undergoing hemodialysis, who developed recurrent hypoglycemia with presentation of cold sweats and disturbed consciousness during treatment with propoxyphene. In uremia, neuroglycopenic manifestations predominate because of autonomic nervous system dysfunction and possibly lack of immediate release of counter-regulatory hormones.³ Therefore,

in uremic patients who suffer from change of consciousness, the differential diagnosis should include hypoglycemia induced by prescribed medications, especially propoxyphene.

Case Report

An 82-year-old woman with diabetic nephropathy in end-stage renal disease undergoing long-term maintenance hemodialysis was admitted to our hospital for permanent catheter (PermCath, Arrow Cannon™ II Plus; Quinton Instrument Co., Seattle, WA, USA)-related infection. Her usual medications included isosorbide-5-mononitrate (20 mg daily), carvedilol (6.25 mg twice daily), hydralazine (10 mg twice daily), nifedipine (20 mg twice daily), and estazolam (2 mg daily). Her blood sugar was controlled by diet, and she had not used any oral antidiabetic drug or insulin for 2 years. The PermCath was removed, and she was treated with antibiotics. A temporary femoral venous catheter was inserted for hemodialysis. The patient complained of intolerable pain over the insertion site

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and was irresponsive to acetaminophen. Therefore, Depain X[®], 1 tablet 4 times daily, was prescribed for pain relief. Each Depain X[®] tablet contains propoxyphene 65 mg and acetaminophen 650 mg.

Five days later, the patient presented with cold sweats and drowsy consciousness in the early morning, with fasting blood glucose of 2.28 mmol/L. The symptoms were relieved after intravenous administration of 50% glucose solution. Meanwhile, plasma immunoreactive insulin (IRI) was elevated to 52.45 pmol/L. Maintenance glucose solution was prescribed after a bolus of 50% glucose solution. Fasting plasma glucose under continuous infusion of 10% glucose solution ranged from 3.17 mmol/L to 5.56 mmol/L. However, fasting hypoglycemia recurred due to withholding glucose solution treatment by the presentation of agitation, cold sweating and drowsy consciousness 10 days after the first episode. A blood glucose concentration of 2 mmol/L and high IRI level of 139.2 pmol/L as well as C-peptide level of 3.51 nmol/L were noted (Figure 1). These findings were consistent with hyperinsulinemic hypoglycemia, with plasma insulin concentration >43 pmol/L and plasma C-peptide >0.2 nmol/L when plasma glucose concentration was <2.5 mmol/L in the fasting state with symptoms.

Abdominal magnetic resonance imaging (MRI) study did not reveal insulinoma or other pancreatic lesions. Cortisol level during hypoglycemia was 563.04 nmol/L (reference range, 138–690 nmol/L). The patient was afebrile, with normal white blood cell counts of 9,400/mm³ and C-reactive protein of 9.6 mg/L (reference range, <10 mg/L). She was fed with normal adult solid diet by mouth thrice a day, and her caloric intake was adequate, with approximately

36 kcal per kilogram per day. She had no alcohol consumption or concomitant liver disease with serum alanine aminotransferase of 14 U/L, aspartate aminotransferase of 19 U/L and total bilirubin of 0.3 mg/dL. Hence, drug-related hypoglycemia was suspected. Depain X[®] was discontinued 4 days after the second episode of hypoglycemia. Upon discontinuation of Depain X[®], blood glucose levels returned to a stable range of 6.11–8.94 mmol/L and the symptoms of hypoglycemia resolved. The follow-up IRI levels were reduced to 20.23 pmol/L and 19.62 pmol/L with fasting plasma glucose concentrations of 6.39 mmol/L and 6.67 mmol/L, respectively (Figure 1). Thereafter, no further episodes of hypoglycemia occurred.

Discussion

The kidney plays an important role in glucose homeostasis and insulin metabolism. Recent findings have indicated that the kidney, in addition to the liver, makes a significant contribution to gluconeogenesis under various conditions. Renal gluconeogenesis accounts for about 40–50% of systemic glucose release in the postabsorptive state of humans. The pathogenesis of spontaneous hypoglycemia with unknown causes in uremia is complex and associated with reduced renal gluconeogenesis, impaired renal insulin degradation and clearance.^{1–4} Hypoglycemia in chronic renal failure patients has various causes and is frequently related to the prescribed medications. Drugs known to induce hypoglycemia include insulin, oral antidiabetic drugs, salicylates,⁵ sulfonamide,⁶ disopyramide⁷ and propoxyphene.^{8–10} Other triggering events such as alcohol consumption, sepsis, chronic malnutrition, acute caloric deprivation, concomitant liver disease, congestive heart failure, and associated endocrine deficiency were not observed in our case.³

It is important to obtain a thorough medication history in uremic patients with hypoglycemia. Side effects of propoxyphene such as dizziness, vomiting, constipation, stomach upset, skin rash, headache and drowsiness are common, but hypoglycemia is unusual. The first case of propoxyphene-induced hypoglycemia was reported by Wiederholt et al.⁸ They described a 57-year-old woman with metastatic cervical cancer and renal failure who experienced recurrent fasting hypoglycemia during treatment with propoxyphene. The hypoglycemia episode with manifestation of focal reversible neurologic disturbance could not be explained by any focal alterations of cerebral vasculature at autopsy. Almirall et al⁹ reported that a 36-year-old man with ankylosing spondylitis, amyloidosis and

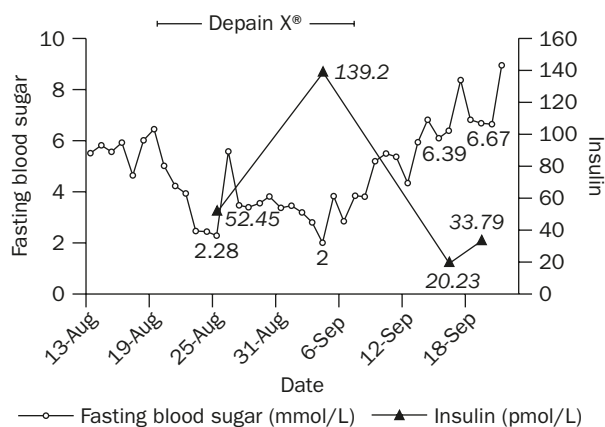


Figure 1. Fasting blood glucose profile (white circles) shows 2 hypoglycemic episodes with elevated insulin levels (black triangles) during administration of Depain X[®] from August 19, 2006 to September 8, 2006. Blood sugar returned to normal range on September 13, 2006 after withdrawal of propoxyphene for 5 days.

chronic renal failure on maintenance hemodialysis developed severe hypoglycemia while being treated with propoxyphene. Another case, reported by Shah et al,¹⁰ was that of a 54-year-old man with chronic renal failure who had recurrent episodes of hypoglycemia during treatment with propoxyphene. Inappropriately elevated plasma insulin, serum C-peptide, and proinsulin levels were also noted. These cases and our patient did not experience any episode of hypoglycemia after withdrawal of propoxyphene.

The temporal association between propoxyphene and hypoglycemia, and the recovery from hypoglycemia upon discontinuation of propoxyphene strongly implicated propoxyphene-induced hypoglycemia in our case. Hyperinsulinemia occurring during treatment and resolving after withdrawal of propoxyphene also indicated the possible potentiation effect of insulin release. The subsequent resolution of hyperinsulinemia and negative abdominal MRI study further excluded the possibility of insulinoma. So far, the true mechanism of propoxyphene-induced hypoglycemia is still obscure.

In conclusion, hypoglycemia is a severe life-threatening complication and should be suspected in any uremic patient with cold sweats, agitation and depressed consciousness. This case report draws the attention to the possibility that propoxyphene might

be responsible for hypoglycemia, especially in uremic patients.

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