

Hypoglycemic Coma in a Hemodialysis Patient Receiving Blood Glucose-Lowering Therapy With the Single Agent Tenueligliptin

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ABSTRACT: Blood glucose management in patients undergoing dialysis is clinically challenging. In this population, most conventional oral hypoglycemic agents are contraindicated, especially from the perspective of pharmacokinetics. Dipeptidyl peptidase-4 inhibitors exert unique pharmacologic actions via glucose-dependent mechanism and have an excellent tolerability profile with a very low risk of hypoglycemia. Furthermore, the literature reports that some dipeptidyl peptidase-4 inhibitors such as tenueligliptin can be administered at the usual dose, regardless of a patient's level of renal impairment. In this article, we report a case of hypoglycemic coma with a blood glucose level of 23 mg/dL. The patient became fully conscious shortly after receiving a glucose injection; however, severe hypoglycemia recurred for approximately 1.5 days. It eventually disappeared on the discontinuation of tenueligliptin, which was the only antidiabetic agent that he had received. The present case may provide deep insights into promoting the safe use of hypoglycemic agents in patients undergoing dialysis.

KEYWORDS: Hemodialysis, hypoglycemic coma, dipeptidyl peptidase-4 inhibitor, pharmacokinetics

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INTRODUCTION

Blood glucose management in dialysis patients is clinically challenging. In this population, most conventional oral hypoglycemic agents such as the sulfonylureas and the biguanides are contraindicated to avoid serious adverse effects and prolonged drug exposure, especially from the perspective of pharmacokinetics.^{1,2} The association between poor glycemic control with risk of hospitalization and death has been clearly demonstrated.³ Dipeptidyl peptidase-4 (DPP-4) inhibitors, a major new class of oral antidiabetic drugs, exert unique pharmacologic actions via a glucose-dependent mechanism and have an excellent tolerability profile with a very low risk of hypoglycemia.⁴ Furthermore, the literature reports that some DPP-4 inhibitors such as tenueligliptin can be administered at the usual dose, even if a person has severely impaired renal function.^{2,5–7} Thus, even among dialysis patients, tenueligliptin is unlikely to cause an extreme decrease in the blood glucose level. Given this background, we report in this article a case of hypoglycemic coma in a hemodialysis (HD) patient. A severe drop in the blood glucose concentration was observed for approximately 1.5 days. However, it eventually disappeared only with the discontinuation of tenueligliptin. The present case may provide deep insights into promoting the safe use of hypoglycemic agents in dialysis patients.

Case Report

A 75-year-old man was transferred to our hospital by ambulance early in the morning because of a severely impaired

consciousness level with a Glasgow Coma Scale of 7. For nearly 5 years at a clinic close to his home, he had uneventfully received twice weekly HD due to diabetic nephropathy. He had been free of serious hypoglycemic episodes for several years. Approximately 40 days before the emergency transportation, he began receiving tenueligliptin at a dose of 20 mg/d because of worsening glycemic control with a glycoalbumin (GA) level of 27.1%. Despite having eaten a comfortable meal on the previous night, his blood test results on his arrival at the hospital revealed a severe hypoglycemic state: 23 and 45 mg/dL in the venous and capillary blood, respectively. Tenueligliptin, a DPP-4 inhibitor, was the only ongoing antidiabetic medication, which he had last taken the previous evening. His other medications and their daily dose were as follows: 75 mg of clopidogrel, 60 mg of nifedipine, 2 mg of doxazosin, 240 mg of furosemide, 20 mg of olmesartan, 5 mg of zolpidem, 3 g of calcium carbonate, and 300 mg of ursodeoxycholic acid. At the time of dialysis, he also received intravenously 6000 units of epoetin alfa, 5 µg of maxacalcitol, and 1 g of levocarnitine chloride. The patient informed us that he had taken these medications the previous evening and taken them exactly as prescribed. Thus, an ordinary cause of severe hypoglycemia was not determined, including the prescription. He became fully conscious shortly after an intravenous injection of glucose. However, the decision to hospitalize him was determined primarily because of significant fluid retention, which was coincidentally revealed by chest computed



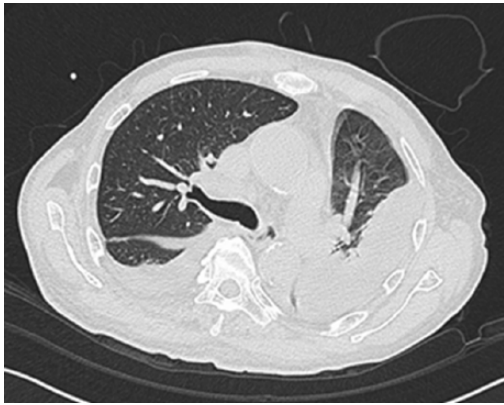


Figure 1. A representative chest computed tomography image. Massive effusions in the pleural and interlobular spaces are delineated.

tomography imaging (Figure 1). At the time of admission, the GA level was reduced to 22.6%.

The problem of anasarca was settled by near-daily HD with little difficulty. His dry weight reduced from 55.0 to 51.0 kg. Thereafter, HD frequency was increased to 3 times weekly. In marked contrast, severe hypoglycemia reemerged immediately following recovery from hypoglycemia and required frequent glucose injections (Figure 2), despite his consuming full meals. Teneagliptin was immediately discontinued, although its causal association with his hypoglycemia was not determined at the time of hospitalization. Doxazosin and nifedipine were subsequently stopped on the following day and 5 days later, respectively, to avoid a blood pressure drop due to the removal of excessive fluid by frequent HD. Zolpidem was discontinued throughout the hospitalization so that the patient's conscious level could be precisely evaluated and because the patient did not call for a hypnotic agent. Incidentally, calcitriol was used as a substitute for maxacalcitol during the hospitalization because of the availability at our facility. After the following afternoon, his overt hypoglycemia eventually disappeared. After 9 days of admission, he was discharged with preprandial blood glucose levels of approximately 120 mg/dL, and no significant hyper- or hypoglycemia.

Discussion

In the present case, the patient's severe hypoglycemia occurred abruptly. The patient became fully conscious shortly after receiving a glucose injection; however, severe hypoglycemia recurred, which eventually disappeared over 1.5 days. Such a time course strongly indicates that the hypoglycemic attacks were caused extrinsically. Teneagliptin was the only antidiabetic agent, which he had started approximately 40 days before experiencing the hypoglycemic coma. It was discontinued immediately after admission. The recovery time exceeded the half-life of teneagliptin (23.6 hours)⁵ by only one-half day, and was reasonable, based on the drug's pharmacokinetics. Three concurrent drugs were incidentally discontinued during hospitalization and may require consideration regarding their

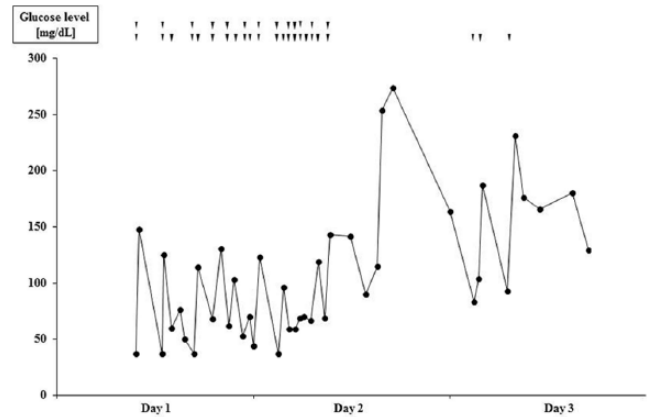


Figure 2. Changes in the blood glucose level over time. The values were measured using capillary blood. The triangles (at the top) indicate the injection of a 20-mL solution containing 50% glucose.

possible effect on glucometabolism. In fact, an add-on study⁸ on the α -blocker doxazosin demonstrated a decrease in 4.1 mg/dL (-2.8%) in fasting plasma glucose; however, it did not document serious hypoglycemia. What is more important is that the patient also took the usual dose of doxazosin on the same evening of the day of admission when hypoglycemic attacks persisted. However, the attacks began to resolve the following day. By contrast, a metabolic study⁹ that used healthy volunteers demonstrated that 15 days of treatment with zolpidem increased the glucose delta area under curve response to the glucose tolerance test (glucose 75 g orally) by 86%. Nifedipine was stopped on the sixth day after admission, whereas the hypoglycemic attacks had disappeared several days earlier. Thus, teneagliptin emerged as the offending drug.

An interim analysis of a 3-year postmarketing surveillance of teneagliptin, which involved more than 10 000 Japanese patients with type 2 diabetes mellitus, was recently published with the conclusion that teneagliptin was well tolerated and improved hyperglycemia.¹⁰ In that investigation, the median administration period was 731 days. However, it is recommended that the dose or dose frequency for most DPP-4 inhibitors be reduced for patients with renal impairment, despite its mild glucose-lowering effect, because the unchanged drugs and active metabolites undergo renal excretion.^{2,11} For instance, sitagliptin must be reduced to one-fourth the usual dose (eg, from 100 to 25 mg/d) when administered to HD patients,¹¹ and the 2012 guide published by the Japanese Society of Dialysis Therapy contraindicates its use for glucose management in diabetic HD patients.² However, it is not fully clear what happens when a patient's renal disorder progresses and thereby increases a patient's exposure to the unchanged drug or its metabolites. One review article surprisingly states, "It should be appreciated that DPP-4 inhibitors do not enhance hypoglycemic risk per se because elevations in glucagon-like peptide-1 and glucose insulinotropic polypeptide modulate insulin and glucagon secretion in a glucose-sensitive manner."¹¹

In Japan, teneligliptin is approved for glycemic control in HD patients without dose adjustment,² based on the low ratio of the unchanged drug eliminated by the kidney (approximately 15%).¹² In fact, 2 clinical studies have recently demonstrated the efficacy and safety of teneligliptin for glycemic control in HD patients at a dose of 20 mg once daily.^{6,7} Otsuki et al⁶ found that the blood glucose and GA levels decreased 21 to 60 mg/dL and 1.7% to 2.3%, respectively, at 28 weeks after teneligliptin administration. In addition, Otsuki et al found no hypoglycemic symptoms or other adverse effects in 14 HD patients who had newly started taking the drug (n = 7), switched from voglibose (n = 4), or switched from vildagliptin (n = 3). Wada et al⁷ observed the blood glucose level every few hours in dialysis patients on HD using a continuous glucose monitoring device and showed significant improvement without severe hypoglycemia on the HD days and on the non-HD days. The GA level dropped from 23.2% to 21.0% among the 10 enrolled HD patients who were drug-naïve (n = 5) or were switched from vildagliptin (n = 2), alogliptin (n = 1), gliclazide (n = 1), or a combination of vildagliptin and gliclazide (n = 1). In line with the findings of these reports, the GA level in the present patient improved from 27.1% to 22.6% during approximately 40 days. This finding indicated that teneligliptin exerted a glucose-lowering action.

Halabi et al⁵ investigated the pharmacokinetics of teneligliptin in patients with various degrees of renal impairment and concluded that dose adjustment may not be needed when teneligliptin is administered to patients with mild, moderate, or severe renal impairment or end-stage renal disease. However, a crucial issue is that their findings are substantially based on a single-dose study, whereas hypoglycemic drugs involve consecutive daily dosing. Halabi found that the area under the plasma concentration-time curve extrapolated to infinity (AUC_{0-∞}) rose to 117.39% and 131.90% in patients with end-stage renal disease, relative to the reference group, when 20 mg of teneligliptin was administered predialysis and postdialysis, respectively, although this increase was unrelated to the level of renal impairment. This finding raises the questions of how the daily administration of teneligliptin alters these parameters and whether it would provoke drug accumulation over time. Nakamaru et al elucidated the pharmacokinetic profiles of teneligliptin using healthy volunteers. They revealed that normally 20% to 34% of the fraction absorbed into the circulation is excreted through the kidneys (66%–80% eliminated by metabolism), whereas the proportion of renal excretion to the applied dose was only 14.8%.¹² In addition, Nakamaru et al found that teneligliptin is significantly cleared through multiple pathways such as renal excretion and metabolism in the human body. Therefore, a disruption in the balance in the elimination pathway, a characteristic feature in dialysis patients, potentially leads to pharmacokinetic alteration and may increase the risk of excessive glucose lowering.

The present case is a possible exception and does not controvert the utility of teneligliptin for dialysis patients. However, it should be recognized that some dialysis patients may develop a serious adverse drug effect, even if the dose is in keeping with those reported in the literature.

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Author Contributions

TM drafted the manuscript. ST and YM made critical revisions. TM, ST, and YI made contributions to the diabetes treatment and dialysis therapy. KS participated in diabetes care, in particular, from the perspective of an endocrinologist. DN provided a detailed review of the contents and structure of the manuscript, which resulted in a significant change to the original document. All authors have read and approved the final manuscript.

Disclosures and Ethics

As a requirement for publication, the authors have provided the publisher with signed confirmation of their compliance with legal and ethical obligations including, but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and (where applicable) the protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this manuscript is unique and not under consideration for publication or published in any other journals and that they have permission from the rights holders to reproduce any copyrighted material. The patient has signed a consent form for participating in this case report and for us to publish it.

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