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【 CASE REPORT 】

Severe and Recurrent Hypoglycemia Caused by Garenoxacin in a Patient not Taking Hypoglycemic Drugs

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Abstract:
Quinolones are known to induce hypoglycemia, although there is no written report of garenoxacin-induced hypoglycemia. We herein report a case of garenoxacin-induced hypoglycemia in a patient not taking hypoglycemic drugs. An 89-year-old Japanese woman with type 2 diabetes and chronic renal insufficiency requiring hemodialysis was admitted to the emergency department in a comatose state. Her serum glucose measured 1 mg/dL on arrival. The patient had not taken any hypoglycemic drugs recently and had never experienced a hypoglycemic episode. She had received a four-day course of garenoxacin treatment before the emergency admission. Clinicians should therefore recognize the potential risk of hypoglycemia during garenoxacin therapy.

Key words: hypoglycemia, quinolones, renal insufficiency

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Introduction

Quinolones have been widely used for the treatment of infectious diseases since the late 1970s. In the Japanese Respiratory Society guideline for the management of pneumonia, garenoxacin is recommended as a second-line option for community-acquired pneumonia. Some quinolones, namely temafloxacin, clinafloxacin, and gatifloxacin, were withdrawn from the market, as they caused serious hypoglycemic or hyperglycemic episodes. These hypoglycemic episodes were usually observed in patients with diabetes on concurrent treatment with oral hypoglycemic agents. We herein report the case of an 89-year-old woman with type 2 diabetes who was not taking hypoglycemic drugs but developed severe and recurrent hypoglycemia after garenoxacin therapy. To our knowledge, this is the first case report of garenoxacin-induced hypoglycemia.

Case Report

An 89-year-old Japanese woman with type 2 diabetes, chronic renal insufficiency requiring hemodialysis, hypothyroidism, and gastroesophageal reflux disease was admitted to the emergency department in a comatose state. With regard to her basic and instrumental activity of daily life, the patient was independent. The patient had not taken any hypoglycemic drugs for several years due to good glycemic control and had never experienced a hypoglycemic episode. She did not drink alcohol. None of her family took hypoglycemic drugs. One year prior to admission, hemodialysis (3 days per week) was started due to diabetic kidney disease. Her dry weight was estimated to be 28.9 kg. At the time of admission, her outpatient drug regimen, which had not been changed for more than a year, consisted of lansoprazole (15 mg/day), calcitriol (0.25 μg/day), levothyroxine (50 μg/day), amezinium metilsulfate (10 mg/day), zopiclone (3.75 mg/day), and epoetin alfa (1,500 units/day, administered twice a week). The patient had consulted her physician 7 days before admission (day -7) with a low-grade fever and vomiting and been prescribed a 4-day course of garenoxacin (200 mg taken orally once a day) and acetaminophen. She had completed the entire prescription. Her caloric intake was decreased during the four days of antibiotic treatment. Five

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Table. **Laboratory Data.**

	2 months before admission, other hospital	On admission, this hospital	Day 2, this hospital	Day 3, this hospital	Day 12, this hospital
Glucose (mg/dL)		1	22	121	119
Insulin (μIU/mL)		0.5	0.7	4	
C-peptide (ng/mL)		3.3 (ref 0.8-2.5)	2.7	10.6	
HbA1c (%)	4.5 (ref 4.7-6.2)	5.3			
GA (%)				22.2 (ref 12.4-16.3)	
BUN (mg/dL)	35.8 (ref 8-20)	46.5	29.1		43.3
Cre (mg/dL)	6.44 (ref 0.4-1.2)	5.93	3.53		5.27
ACTH (pg/mL)			29.5 (ref 7.2-63.3)		
Cortisol (μg/dL)			39.3 (ref 4.5-21.1)		
IGF-1 (ng/mL)			46 (ref unknown)		
TSH (μIU/mL)		4.29 (ref 0.5-5)			
free-T4 (ng/dL)		1.74 (ref 0.9-1.7)			
Insulin antibody		not detected			
Garenoxacin concentration (μg/mL)		4.79	2.97	1.83	

HbA1c: glycated hemoglobin, GA: glycoalbumin, BUN: blood urea nitrogen, Cre: creatinine, ACTH: adrenocorticotropic hormone, IGF-1: insulin-like growth factor-1, TSH: thyroid stimulating hormone, free-T4: free thyroxine

days and three days before admission (days -5 and -3), hemodialysis was performed as usual. The patient's capillary blood glucose level was 129 mg/dL at the end of hemodialysis on day -5.

On the day of admission, the patient presented to our emergency department due to nausea at 1:00 am. The symptom improved spontaneously, and she went home. Her blood glucose level was not checked during her first visit to the emergency department. At 10:00 am, the patient was found unresponsive at home and was transferred to the emergency department. On arrival, her serum glucose measured 1 mg/dL (5 mg/dL with arterial blood), and she received a 20 g bolus of intravenous dextrose. She became alert soon after dextrose supplementation, and her serum glucose increased to 248 mg/dL after 2 hours. The results of admission laboratory tests were normal, except for an extremely low blood glucose level, an elevated white blood cell count, and renal insufficiency (Table). Whole-body computed tomography (CT) showed no abnormal findings that could explain the coma and hypoglycemia. A blood culture was negative, but urine culture was positive for extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*. The patient was admitted to our hospital for observation and hemodialysis.

The patient's capillary blood glucose measured 129 mg/dL at 6 hours and 105 mg/dL at 10 hours after admission. Hemodialysis was performed without any hypoglycemic episodes in the evening on the day of admission. A continuous infusion of 7.5% dextrose was initiated during the night. However, her serum blood glucose decreased to 22 mg/dL the next morning. Although the patient was alert, she received another 20 g bolus of intravenous dextrose, and an infusion of dextrose was started. By hospital day 3, the hypoglycemic episodes had resolved. The rate of dextrose infusion was decreased and finally discontinued. All previous drugs were continued. The patient's caloric intake stabilized, and her capillary blood glucose before meals ranged between 94 and 195 mg/dL. She was discharged on hospital day 16.

Discussion

We detected two important clinical issues. First, garenoxacin can cause severe hypoglycemia. Although the onset of hypoglycemia in relation to garenoxacin administration suggests that the hypoglycemic coma was drug-induced, other potential factors should be discussed. The CT scan did not rule out the existence of an insulin-producing tumor; however, low insulin levels confirm that this was unlikely. Adrenal insufficiency was ruled out due to normal cortisol and adrenocorticotropic hormone levels. Although the patient had a low calorie intake for a few days, it is difficult to conclude that the low calorie intake was the major cause of severe hypoglycemia. To assess the possibility of an adverse drug reaction, we applied the Naranjo probability scale (1). The scale consists of 10 questions, and the probability is assigned by a score of definite (score more than 9), probable (score 5-8), possible (score 1-4), or doubtful (score 0). According to the scale, at least, a probable relationship exists between hypoglycemia and garenoxacin (score 5). Multiple mechanisms explaining how quinolones cause hypoglycemia have been suggested. One major hypothesis is that quinolones stimulate insulin secretion from the pancreatic beta cells (2). In our case, serum C-peptide immunoreactivity (CPR) was slightly elevated, but the insulin levels were low. Slightly elevated CPR is partially explained by impaired clearance due to renal insufficiency. It was difficult to evaluate how much the observed CPR and insulin levels contributed to the hypoglycemia, especially with the patient's extremely low glucose levels. Compensatory mechanisms, such

as glycogenolysis, usually are activated when hypoglycemia occurs; however, this response may be diminished in patients with diabetes, a poor oral intake, acute illness, or an advanced age (3). All of these factors were present in our patient, which may have exacerbated the hypoglycemia.

Second, garenoxacin-induced hypoglycemia can happen even in patients who are not taking hypoglycemic drugs. Drug interactions between quinolones and hypoglycemic agents have been reported (4); however, our patient was not taking any hypoglycemic drugs. The elimination of garenoxacin partially involves the renal pathway; therefore, renal insufficiency probably played an important role in this case. As shown in (Table), we measured the garenoxacin concentration several times. The removal of garenoxacin by hemodialysis is reported to occur at a rate of 1.5% to 11.5% (5). Aoyama et al. reported that administration of 200 mg garenoxacin once daily in 6 patients undergoing maintenance hemodialysis resulted in an average maximum plasma garenoxacin concentration of 3.0±1.12 μg/mL (5). Despite a 72-h interval since the last medication, the garenoxacin concentration in our patient was higher than that reported value, suggesting that accumulation may occur in patients with renal insufficiency after multiple administrations, which can lead to adverse reactions.

Several case reports have indicated that quinolone users face significant risk of severe hypoglycemia (3, 6-8). A recent cohort study from Taiwan showed that moxifloxacin, levofloxacin, and ciprofloxacin were associated with a higher risk of hypoglycemia and hyperglycemia than macrolides and cephalosporins (9). Furthermore, renal insufficiency, sepsis, and hypoglycemic drug therapy were significantly associated with hypoglycemic episodes after gatifloxacin or levofloxacin therapy (10). In our case, renal insufficiency was the only corresponding risk factor, although infection might also affect hypoglycemia. The negative blood culture findings might have been due to the prior administration of garenoxacin.

In conclusion, this case shows that administration of garenoxacin can cause severe hypoglycemia even in patients not taking hypoglycemic drugs. Renal insufficiency, a history of diabetes, poor nutrition, and geriatric age are identified as risk factors associated with severe hypoglycemia when using garenoxacin. It is highly recommended that clinicians recognize the potential risk of severe hypoglycemia during garenoxacin therapy, even in patients not taking hypoglycemic drugs. Once severe hypoglycemia occurs, admission for the regular monitoring of blood glucose and continuous dextrose supplementation is essential until the hypoglycemia has completely been resolved.

The authors state that they have no Conflict of Interest (COI).

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