INTERNAL MEDICINE

□ CASE REPORT □

Hypoglycemic Coma Induced by the Use of Succinic Acid Cibenzoline in Frail Late-stage Elderly Subjects

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Abstract

Succinic acid cibenzoline (CZ) is an antiarrhythmic agent often used for the treatment of tachyarrhythmia. However, hypoglycemia should be avoided in the treatment of diabetes. We herein report two late-stage elderly subjects who experienced a severe and prolonged hypoglycemic coma after the usage of CZ. These cases suggest that, when CZ is administered to elderly subjects with renal dysfunction and/or frailty, we should be aware of the possibility that this medicine may induce hypoglycemia and should adjust the dose as appropriate and monitor the concentration of CZ to avoid severe hypoglycemia.

Key words: succinic acid cibenzoline, hypoglycemic coma, drug concentration

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Introduction

Hypoglycemia is induced by the overuse of various anti-diabetic drugs, including insulin and oral anti-diabetic drugs, as well as by a variety of concomitant diseases, including insulinoma, insulin autoimmune syndrome and adrenal insufficiency. When subjects suffer from hypoglycemia, they usually notice it with warning symptoms such as cold sweating and/or palpitation, which are induced by the secretion of various counter-regulatory hormones such as catecholamine, but they sometimes remain unaware of their condition without any symptoms due to a lack of counter-regulatory hormones, leading to life-threatening hypoglycemic coma (1-3). In addition, hypoglycemia leads to various clinical problems, such as fundus hemorrhaging, acute coronary syndrome and unaware hypoglycemia. Therefore, in practical medicine, we should take care to avoid inducing hypoglycemia when treating diabetes.

Succinic acid cibenzoline (CZ) is an antiarrhythmic agent often used to treat tachyarrhythmia. In practical medicine, this drug is administrated particularly frequently in elderly subjects because the frequency of arrhythmia is higher in these subjects than in younger ones. In addition, catheter ablation therapy is often selected for the treatment of arrhythmia in young subjects, but not in elderly subjects, which also explains the reason why CZ is administered relatively often in elderly subjects.

In addition, it is known that this medicine functions as an ATP-sensitive potassium (KATP) channel blocker and thereby facilitates endogenous insulin secretion from pancreatic β-cells, which can lead to the onset of hypoglycemia (4, 5). We herein report two frail, late-stage elderly subjects who experienced a severe and prolonged hypoglycemic coma after the administration of CZ.

Case Report

Table 1 shows the clinical characteristics of two cases who experienced severe and prolonged hypoglycemic coma after the usage of CZ. The plasma glucose levels in Cases 1 and 2 were as low as 18 and 29 mg/dL, respectively. Both were elderly subjects with mild renal dysfunction and frail status. Skin turgor was diminished in both cases. Case 1 had type 2 diabetes and was being treated with mitiglinide and voglibose, whereas Case 2 was not diabetic. Both cases had

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Table 1. Clinical Characteristics of 2 Cases with Severe Hypoglycemia Induced by CZ.

	Case 1	Case 2
Age (years old)	82	91
Gender	male	female
Height (cm)	170.0	145.5
Body weight (kg)	51.0	35.5
Body mass index (kg/m^2)	17.6	14.9
Plasma glucose level (mg/dL)	18	29
IRI (μU/mL)	28.7	18.0
HbA1c (%)	5.2	4.5
Cre (mg/dL)	1.4	0.82
BUN (mg/dL)	31	31
eGFR (mL/min/1.73m^2)	37.9	41.4
AST (U/L)	38	12
ALT (U/L)	43	22
ACTH (pg/mL)	30.6	24.6
Cortisol (μg/dL)	26.5	15.3
Usage dose of CZ (mg/day)	300	200
Blood concentration of CZ (ng/mL)	671	1,551
Duration of hypoglycemia (days)	2	3

Table 2. Time Course of Plasma Glucose and Insulin Levels after Stopping CZ.

Case 1	day 1	day 3	day 7
Plasma glucose level (mg/dL)	18	123	162
IRI (μU/mL)	28.7	7.1	no data
Blood concentration of CZ (ng/mL)	671	no data	no data
Case 2	**day 1**	**day 3**	**day 7**
Plasma glucose level (mg/dL)	33	143	95
IRI (μU/mL)	14.4	6.0	2.0
Blood concentration of CZ (ng/mL)	1,551	1,074	<19

been taking CZ for over three years before this instance of severe hypoglycemia. In addition, severe hypoglycemia together with sympathetic symptoms had not been observed before this instance of severe hypoglycemia.

We first ruled out the possibility of adrenal insufficiency based on the blood test results (Table 1). We assumed that the likelihood of insulinoma or insulin autoimmune syndrome was low in both cases since while we had failed to exclude the possibility of insulinoma and insulin autoimmune syndrome based on the findings at admission, the insulin level had decreased a few days after stopping CZ without any special treatment in both cases (Table 2). In Case 1, since abdominal computed tomography (CT) was not performed and the insulin antibodies were not measured, we failed to rule out insulinoma and insulin autoimmune syndrome at this point. In Case 2, however, since there were no neoplastic lesions in the pancreas on abdominal CT and the insulin antibody levels were negative, we ruled out the possibility of insulinoma and insulin autoimmune syndrome at this point.

We then explored the possibility of hypoglycemic coma induced by the usage of CZ. Cases 1 and 2 had been receiving 300 and 200 mg/day of CZ. While the therapeutically effective trough concentration of CZ is thought to be 70-250 ng/mL, the blood concentration of CZ in Cases 1 and 2 peaked at 671 and 1,551 ng/mL, respectively. Thus, the blood concentrations of CZ in both subjects were at toxic levels and were much higher than the therapeutically effective concentrations. In addition, neither patient had been receiving any other medication that might have contributed to severe hypoglycemia.

Based on these findings, we concluded that the hypoglycemic coma in both subjects was induced by the usage of CZ. We therefore stopped CZ in both cases and also discontinued mitiglinide in Case 1. In addition, we started glucose infusion for recovery from the hypoglycemic coma. However, the hypoglycemia persisted for 2 days in Case 1 and 3 days in Case 2. Table 2 shows the time course of the plasma glucose and insulin levels after stopping CZ. As shown in Table 2, after stopping CZ, the plasma glucose level increased and the insulin level decreased in both cases. In Case 2, we examined the time course of the CZ concentration and found that the CZ concentration gradually decreased. Both patients were ultimately discharged without any sequelae.

Discussion

Both cases were frail, late-stage elderly subjects with renal dysfunction, presumably due to dehydration. The renal function in elderly subjects can be easily deteriorated by subtle changes under various conditions, such as dehydration. We should be aware of the possibility that the blood concentration of CZ can be easily increased in subjects with renal dysfunction and/or frail status because CZ is excreted mainly via the kidney. Although many physicians know that CZ can cause hypoglycemia by accelerating endogenous insulin secretion, the present cases suggest that the possibility of CZ-induced hypoglycemia is relatively high among elderly subjects, particularly those with renal dysfunction and/or a frail status. We should also be aware of the possibility that the concentration of CZ can be elevated in subjects with heart failure (6). In addition, since CZ in metabolized by cytochrome P450 (CYP), we should be careful of the interaction with other drugs in practical medicine in order to avoid inadvertently increasing the CZ concentration in patients. Of note: Case 1 had been taking the same amount of mitiglinide for over one year but had never experienced hypoglycemia. Therefore, although we cannot completely exclude the possibility that over-dose of mitiglinide was also involved in the onset of severe hypoglycemia in Case 1, we believe that the administration of CZ in addition to mitiglinide probably contributed to the severe hypoglycemia.

Several case reports have described the onset of hypoglycemia (blood glucose level ≤50 mg/dL) induced by the usage of CZ (7-11). All 5 subjects in these reports were more than 60 years old, and the average age was 72 years old.

The average blood glucose levels in these 5 subjects was 37 mg/dL (7-11). Two of the subjects had severe hypoglycemia (blood glucose level ≤30 mg/dL) (10, 11). One subject was 71 years old, and the blood glucose level was 28 mg/dL (10). Another subject was 89 years old, and the blood glucose level was as low as 18 mg/dL (11). The findings from the present two cases and these previously reported subjects suggest that we should be particularly careful when prescribing CZ in elderly subjects. Among the 5 subjects in these previous reports (7-11), 4 had chronic renal failure (Cre ≥2 mg/dL), and both subjects with severe hypoglycemia had severe chronic renal failure (10, 11). The Cre level in 1 subject was as high as 3.59 mg/dL, and another subject was receiving hemodialysis. These data suggest that subjects with renal failure are at particular risk of severe hypoglycemia. Furthermore, all five subjects in these reports (7-11) were taking diuretics, which can cause dehydration, especially in elderly subjects. Therefore, we should be particularly careful when prescribing CZ in elderly subjects with chronic renal failure and/or using diuretics. In addition, in our cases, hypoglycemia persisted for 2 days in Case 1 and 3 days in Case 2 after stopping CA, although both patients were eventually discharged without sequelae. Another report found that CZ-induced hypoglycemia is prolonged compared with other forms, despite treatment (11). The present and previous findings suggest that we should carefully observe subjects even after stopping the prescription of CZ.

In conclusion, when we use CZ in elderly subjects with renal dysfunction and/or frail status, we should be aware of the possibility that this medicine might induce hypoglycemia and should adjust the dose of medicine as appropriate and monitor its concentration in order to avoid severe hypoglycemia and various clinical problems such as fundus hemorrhaging, acute coronary syndrome and unaware hypoglycemia. We believe that the findings in this report call for attention from a clinical point of view.

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

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