

[ CASE REPORT ]

## Relapsing Hypoglycemia Associated with Hypocarnitinemia Following Treatment with Cefcapene Pivoxil in an Elderly Man

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### Abstract:

Pivoxil-containing cephalosporins can result in symptomatic hypocarnitinemia in children. We herein report a case of an 85-year-old man at risk of carnitine deficiency who developed relapsing symptomatic hypoglycemia after treatment with cefcapene pivoxil for urinary tract infection. On admission, laboratory tests showed low blood carnitine concentrations with low normal blood ketone levels. The patient was successfully treated by the oral administration of levocarnitine and dietary modification, including aggressive consumption of meat and dairy products, and remained symptom-free for nine months after the correction of carnitine concentrations. Healthcare providers should be cautious when prescribing pivoxil-containing antimicrobials to patients at high risk of hypocarnitinemia.

**Key words:** carnitine, cefcapene pivoxil, hypoglycemia

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### Introduction

Carnitine is an important nutrient for lipid metabolism, as it plays a role in energy production from beta-oxidation by transporting long-chain fatty acids into mitochondria (1). Several drugs - especially valproate and pivaloyl-containing antibiotics - decrease carnitine concentrations by increasing the carnitine excretion into the urine and are reported to cause hypoglycemia, mainly in children (2).

We herein report a case of an elderly Japanese man at high risk of carnitine deficiency whose hypocarnitinemia-induced hypoglycemia was likely triggered by a pivoxil-containing cephalosporin.

### Case Report

This case report followed the CARE guidelines (3), and informed consent for the publication of this report was obtained from the patient. Under our institutional policy, approval of the institutional review board is not required for case reports.

An 85-year-old Japanese man with a recent history of surgery for gastric cancer and laryngeal chondrosarcoma was brought to our emergency department (ED) due to excessive diaphoresis lasting 1 hour. Three days earlier, he had started oral cefcapene pivoxil hydrochloride to treat a suspected urinary tract infection noted by the local urologist; the patient was on intermittent self-catheterization for flaccid neurogenic bladder and benign prostatic hyperplasia. His regular medications included silodosin, a highly uroselective alpha-adrenergic receptor antagonist, distigmine, a parasymphomimetic drug for neurogenic bladder, and magnesium oxide for chronic constipation. He had no family history of diabetes and was not taking any medications that caused hypoglycemia. The patient reported that his last meal had been rice noodles at five hours prior to ED arrival. He denied any recent consumption of tobacco or alcohol.

Further discussion about his diet revealed that the patient had become selective about foods following the total loss of his teeth and had rarely consumed meat or dairy products in recent years. Four months prior to this episode, he had undergone laparoscopic distal gastrectomy with type D1 lymphadenectomy followed by Billroth II reconstruction for

**Table 1. Laboratory Findings on Admission.**

Complete blood count		Glucose	58 (70-109) mg/dL
White blood cells	5,800 (3,200-8,500) / $\mu$ L	L-lactate	22.8 (4-16) mg/dL
Red blood cells	363 (380-500) $\times 10^4$ / $\mu$ L	Insulin	9.5 (5.0-10.0) $\mu$ U/mL
Hemoglobin	10.8 (11.5-15.0) g/dL	C-peptide	6.21 (0.67-2.48) ng/mL
Platelet	32.6 (13.0-34.9) $\times 10^4$ / $\mu$ L	Cortisol	18.36 (ND) $\mu$ g/mL
		Total ketones	31 ( $\leq 130$ ) $\mu$ mol/L
Blood chemistry		Acetoacetate	3 ( $\leq 55$ ) $\mu$ mol/L
Total protein	7.0 (6.7-8.3) g/dL	$\beta$ -hydroxybutyrate	28 ( $\leq 85$ ) $\mu$ mol/L
Albumin	3.2 (4.0-5.0) g/dL	Anti-insulin antibody	<0.4 (<0.4) U/mL
Aspartate aminotransferase	38 (0-35) U/L	Urinalysis	
Alanine aminotransferase	29 (0-35) U/L	Microscopic urinalysis	10-19 (1-4) Leukocytes/ high power field
Creatine phosphokinase	62 (62-287) U/L	Ketones	Negative (Negative)
Blood urea nitrogen	14.1 (8.0-22.0) mg/dL	Arterial blood gas analysis (room air)	
Creatinine	0.75 (0.6-1.1) mg/dL	pH	7.448 (7.35-7.45)
Sodium	140 (138-146) mEq/L	Partial pressure of carbon dioxide	32.0 (37.0-44.0) mmHg
Potassium	2.9 (3.6-4.9) mEq/L	Partial pressure of oxygen	151.1 (74.0-104.0) mmHg
Chloride	105 (99-109) mEq/L	Bicarbonate	21.6 (22.0-26.0) mmol/L
Phosphorus	2.5 (2.5-4.7) mg/dL		
Vitamin B <sub>1</sub>	41 (24-66) ng/mL		
Hemoglobin A1c	5.4 (3.1-6.0) %		

stage IIIB gastric cancer, and then received total laryngectomy with permanent tracheostomy for grade 2 laryngeal chondrosarcoma. After being discharged, he became withdrawn and stayed home, where his selective eating behavior worsened - he consumed an exclusively carbohydrate diet, eliminating meats and vegetables.

On arrival at the ED, the patient was drowsy (grade II-10 according to the Japan Coma Scale, eye-opening possible upon stimulation) and appeared cachexic. His vital signs were stable with a body temperature of 35.3°C, pulse of 60 per minute, respiratory rate of 17 breaths per minute, oxygen saturation of 100% at room air, and blood pressure of 122/62 mmHg. His body mass index was 19.5 kg/m<sup>2</sup>. Physical examination findings were unremarkable, except for the permanent tracheostomy and decreased muscle volume in the lower extremities, suggestive of disuse atrophy due to a sedentary lifestyle. A rapid finger-stick test for capillary glucose measurement by the Hagedorn-Jensen method (Glutest ai; Sanwa Kagaku Kenkyusha, Nagoya, Japan) indicated hypoglycemia (47 mg/dL). Although intravenous injection of 40 mL 50% glucose transiently relieved his symptoms, the patient was admitted to the general internal medicine ward for further testing and treatment. He received continuous intravenous infusion of 10% glucose solution and piperacillin-tazobactam intravenous injections every 6 hours for possible hypoglycemia as a manifestation of urosepsis suspected on presentation.

Basic laboratory tests and an arterial blood gas analysis performed before bolus injection of dextrose at the ED showed the following: hyperventilation-induced acute uncompensated primary respiratory alkalosis with secondary non-anion gap metabolic acidosis (Table 1), mild anemia (hemoglobin 10.8 g/dL), hypopotassemia (2.9 mEq/L) most likely due to

respiratory alkalosis, and low blood glucose (58 mg/dL using the glucose oxidase electrode method). Other abnormal findings included mildly increased levels of CRP (2.13 mg/dL), L-lactate (22.8 mg/dL), and pyuria (10-19 leukocytes per high power field by microscopic urinalysis). Urinary ketones were negative. The fasting blood test revealed a normal insulin level (9.5  $\mu$ U/mL) and a slightly elevated level of C-peptide (6.21 ng/mL). Table 1 shows the complete laboratory findings. Computed tomography (CT) of the head was unremarkable, and chest and abdominal CT without contrast did not reveal any sources of infection that could cause sepsis-induced hypoglycemia or any pancreatic tumor or tumorous lesion outside the pancreas suggestive of non-islet cell tumor hypoglycemia. The measurement of anti-insulin antibody in the blood was negative.

One day after admission, the patient became asymptomatic with stable blood glucose levels, and his hypopotassemia and respiratory alkalosis resolved with intravenous maintenance fluid therapy that included 15 mEq of potassium replacement. Piperacillin-tazobactam was discontinued after the second dose, as his stable clinical course excluded urosepsis. He was discharged on day six, after nutrition counseling recommending a standard dietary modification program of small, frequent meals, with a tentative diagnosis of late dumping syndrome based on his medical history, mildly elevated C-peptide level, and normal insulin concentration (Table 1). The medical team decided not to perform provocation tests for the objective assessment of dumping syndrome, namely the oral glucose tolerance test and mixed-meal tolerance test, until the patient's response to dietary adjustments had been determined (4).

However, despite the patient faithfully adhering to the dietary adjustments, his hypoglycemia episodes with excessive

**Table 2. Carnitine Concentrations before and after Treatment with Levocarnitine Supplementation.**

	On admission*	7 days before treatment	7 days post-treatment	2 months after discontinuation of treatment	Reference range
Total carnitine	13.7	31.2	87.6	70.6	45-91 (μmol/L)
Free carnitine	12.6	24.9	66.9	55.8	36-74 (μmol/L)
Acyl carnitine	1.1	6.3	20.7	14.8	6.0-23.0 (μmol/L)

\*Four weeks prior to treatment.

diaphoresis frequently recurred for a period of four weeks, within a few hours after meals. Further analyses of blood samples obtained on admission and four weeks later revealed persistent decreased levels of total carnitine and free and acyl carnitine (Table 2), suggesting the possibility of hypocarnitinemia-induced hypoglycemia. Blood ketones, including β-hydroxybutyrate, in samples obtained on admission were low (Table 1), although high levels were expected as a normal response to hypoglycemia. This finding is consistent with the absence of hyperketosis typically observed in a state of hypocarnitinemia.

Due to a high suspicion of hypocarnitinemia-induced hypoglycemia, 1,500 mg oral levocarnitine was administered daily for 1 week and then reduced to 750 mg daily for the next week, which completely resolved the relapsing hypoglycemia. The patient was strongly advised to consume meat and dairy products in addition to the recommended small, frequent meals. Table 2 shows the changes in blood carnitine concentrations before and after treatment. After correcting the blood carnitine levels and modifying diet, the patient remained stable and free from relapsing hypoglycemic attacks for nine months.

## Discussion

We encountered a man who likely developed hypocarnitinemia-induced hypoglycemia triggered by the administration of a pivoxil-containing cephalosporin. We based the diagnosis of symptomatic carnitine deficiency on the following: a free carnitine concentration <20 μmol/L and the rapid resolution of symptoms with levocarnitine treatment, which satisfied 2 of the recently proposed criteria for a clinical diagnosis (5).

Several risk factors for developing secondary hypocarnitinemia have been reported, including malnutrition, long-term use of parenteral nutrition or carnitine-free enteral feeding products, increased urinary excretion due to medications like valproate and pivaloyl-containing antibiotics, and low carnitine storage stemming from muscle atrophy (2, 5). The present patient was a frail, sarcopenic man with a history of gastrectomy and laryngectomy and a withdrawn, sedentary lifestyle. In addition, he avoided consuming meat and dairy products, which are two major sources of dietary carnitine (1, 2). Such lifestyle habits can cause a low storage of carnitine in the muscle, which may have been a predispos-

ing factor to the development of low blood carnitine levels. Pivoxil-containing cephalosporins cause hypocarnitinemia by increasing the carnitine excretion in urine as pivaloylcarnitine, an esterified form with pivalate that is released from metabolized antibiotics (2). Thus, the administration of cefcapene pivoxil for urinary tract infection exacerbated his hypocarnitinemia, resulting in symptomatic hypoglycemia, which we believe is the most likely interpretation for this case.

At the onset of hypoglycemia, our patient had a normal but slightly high insulin concentration ( $\geq 3$  μU/mL) relative to hypoglycemia (6) and a high C-peptide level. The observed pattern of these findings in symptomatic hypoglycemia, under a reportedly fasting state in the absence of insulin secretagogues, is consistent with endogenous hyperinsulinism, such as insulinoma, non-insulinoma pancreatogenous hypoglycemia, insulin autoimmune syndrome, and late dumping syndrome (6). Based on laboratory and imaging test results and the patient's clinical course, we concluded that serious conditions liable to cause hypoglycemia, including urosepsis, adrenal insufficiency, and insulinoma, were unlikely. Non-insulinoma pancreatogenous hypoglycemia syndrome, a rare condition that can cause non-ketotic, hyper-insulinemic post-prandial hypoglycemia and an important differential diagnosis of insulinoma when imaging tests are negative for localizing pancreatic lesions, was also deemed unlikely because gastric bypass surgery does not typically precede this condition (7). An undetectable level of anti-insulin antibody denied the possibility of insulin autoimmune syndrome.

Although uncommon, hypocarnitinemia-induced hypoglycemia is a widely acknowledged side effect of pivaloyl-containing antibiotics and is typically observed in children, especially infants (5). At the time of writing, only 1 other adult case had been reported: an 85-year-old woman with a history of cerebral infarction and long-term nasogastric feeding who developed excessive diaphoresis and coldness of limbs due to documented hypoglycemia (glucose level of 42 mg/dL) the same day as receiving cefcapene pivoxil hydrochloride for acute bronchitis (8). Her hypoglycemia resolved within one day after discontinuing the suspect antibiotic and multiple glucose treatments. Although hypocarnitinemia-induced hypoglycemia was highly suspected due to the absence of other pathologies that could explain the low blood glucose levels, blood carnitine measurements and carnitine

supplementation were not performed. Thus, the present case may be the first well-documented adult case of hypocarnitinemia-induced hypoglycemia triggered by pivaloyl-containing antibiotics.

Several limitations associated with the present case report warrant mention. First, we did not perform a postprandial evaluation using provocation tests because their use for diagnosing dumping syndrome is controversial due to the limited data available (4). Although the clinical presentation and laboratory results in our case were consistent with those of late dumping syndrome, the patient's poor response to the dietary modifications for a month along with his documented low carnitine levels and good response to carnitine supplementation precluded their implementation. However, rather than completely excluding the possibility of dumping syndrome, we acknowledge that the patient's post-gastric bypass status, in conjunction with the documented hypocarnitinemia, would have contributed to the development of symptomatic hypoglycemia. Second, the fasting elevated C-peptide level in our case was higher than expected relative to the slightly elevated insulin concentration simultaneously measured. Despite the absence of a severely impaired renal function, a major cause for the observed discordant (extent of) increases between insulin and C-peptide levels (9), we were unable to determine the underlying mechanism for this finding. Third, non-islet cell tumor hypoglycemia, a rare but serious paraneoplastic syndrome, is an important alternative etiology that can present with hyper-insulinemic hypoglycemia (9), especially given the recent history of double primary cancer in our case. We did not measure the insulin-like growth factor (IGF)-I or IGF-II levels, or more specifically the levels of high-molecular-weight pro-IGF-II, the primary etiology that causes hypoglycemia (9). However, we believe this is acceptable since there were no clinical findings suggestive of recurrence, such as large residual tumorous lesions, on whole-body CT, and the refractory hypoglycemia was completely resolved after carnitine supplementation.

In summary, the administration of pivoxil-containing cephalosporins to patients with underlying risk factors for carnitine deficiency can induce symptomatic hypoglycemia

due to hypocarnitinemia. Healthcare providers should be cautious when prescribing pivaloyl-containing antibiotics to high-risk patients, since it may result in relapsing hypoglycemia that cannot be managed solely by standard glycemic control methods.

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

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