Clinical Features of Carnitine Deficiency Secondary to Pivalate-Conjugated Antibiotic Therapy

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Objective To examine the clinical features and risk factors of secondary carnitine deficiency due to long-term use of pivalate-conjugated antibiotics (PCAs).

Study design We retrospectively investigated the age, clinical manifestations, PCA administration period, and background of 22 patients who showed a decrease in free carnitine (C0; ≤20 μmol/L) concomitant with an increase in pivaloyl carnitine (detected as C5-acylcarnitine) on acylcarnitine analysis with tandem mass spectrometry. Administration of PCAs was confirmed in all cases.

Results The patients ranged in age from 2 months to 42 years (median, 1 year, 11 months). One patient was aged <1 year, 10 patients were aged 1 year, 1 patient was aged 2 years, and 10 patients were aged ≥3 years. Nine patients had known underlying disease. Fourteen patients developed acute encephalopathy, 13 with accompanying hypoglycemia. Four patients presented with hypoglycemia without signs of encephalopathy. C0 values ranged from 0.25 to 19.66 μmol/L (median, 1.31 μmol/L); C5-acylcarnitine values, from 0.43 to 11.92 μmol/L (median, 3.23 μmol/L). There was no correlation between the PCA administration period and C0 level. Ten patients developed the symptoms after PCA administration for ≥14 days, whereas 6 patients showed symptoms after PCA administration for <14 days.

Conclusion Carnitine deficiency resulting from PCA treatment was most frequently observed in 1-year-old infants. Most patients manifested acute encephalopathy and/or hypoglycemia. Some patients developed carnitine deficiency after PCA administration for <14 days. *(J Pediatr 2016;173:183-7)*.

Antibiotics containing a pivoxil group are prodrugs in which a pivoxil moiety is bound to improve absorption from the intestine. In Japan, these drugs include cefditoren pivoxil, cefcapene pivoxil, cefteram pivoxil, and tebipenem pivoxil. The absorbed antibiotics are rapidly hydrolyzed into pivalate and active antibiotics within mucosal cells of the small intestine. Most of the pivalate binds to free carnitine (C0) in blood, resulting in the formation of pivaloyl carnitine, which is excreted in urine. Consequently, C0 in blood is depleted, leading to secondary carnitine deficiency.[1] Although pivaloyl carnitine can be detected as C5-acylcarnitine (C5) in acylcarnitine analysis using tandem mass spectrometry (MS/MS), C5 also has an isoform of isovalerylcarnitine, which is a diagnostic indicator of isovaleric acidemia. Discrimination between these conditions can be made by urine organic acid analysis using gas chromatography–mass spectrometry (GC/MS).[2]

Carnitine has a low molecular weight (161.2), is water-soluble, and is essential for the transport of long-chain fatty acids from the cytoplasm to the mitochondria.[3] In the cytoplasm, long-chain fatty acids are converted to long-chain acyl-CoA. Long-chain acyl-CoA is converted to its respective acylcarnitines at the outer mitochondrial membrane. The acylcarnitine is transported into mitochondria, where acylcarnitines are reconverted to acyl-CoA at the inner mitochondrial membrane and provide as the substrate for β-oxidation. In carnitine deficiency, long-fasting fever or infections, including upper respiratory tract infection or gastroenteritis, accompanying a hypercatabolic state commonly result in symptoms of β-oxidation defects, such as hypoglycemia and skeletal muscle symptoms.[3,4] Frequently observed laboratory findings include nonketotic hypoglycemia, hepatic dysfunction, and mild to moderate hyperammonemia.

Sporadic cases of secondary carnitine deficiency due to long-term oral administration of pivalate-conjugated antibiotics (PCAs) have been reported, mainly in the pediatric population.[2,5-8] All 4 PCAs contain a single pivoxil moiety, and as such have similar effects on carnitine consumption.

Administration of PCAs for >14 consecutive days is cautioned against in the Japanese drug information for PCAs. The epidemiology, clinical features, and

C0	Free carnitine
C5	C5-acylcarnitine
CDSP	Systemic primary carnitine deficiency
GC	Gas chromatography
MS	Mass spectrometry
PCA	Pivalate-conjugated antibiotic

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risk factors of patients with secondary carnitine deficiency are not well understood, however. In the present study, we investigated the circumstances and clinical manifestations of 22 patients with secondary carnitine deficiency due to oral PCA therapy.

Methods

Acylcarnitine analysis was performed at Shimane University. A total of 13 451 patients with suspected fatty acid oxidation defects or organic acidemia on the basis of their clinical symptoms were investigated for acylcarnitine between April 2004 and December 2012; fatty acid oxidation disorder or organic acidemia was diagnosed in 2% of these patients. In this study, 22 patients demonstrating an increase in C5 and a decrease (≤20 μmol/L) in C0 were investigated retrospectively. Isovaleric acidemia was excluded through urine organic acid analysis using GC/MS, and oral administration of PCAs was confirmed. The age at onset, clinical manifestations, duration of oral PCA administration, and underlying medical conditions were investigated. This study was approved as a retrospective epidemiologic research study by the Institutional Review Board of Shimane University Faculty of Medicine.

Acylcarnitines were analyzed using dried blood spot with MS/MS in accordance with standardized newborn screening protocols.[9] Serum samples were prepared as described previously.[9] C0 was measured with butylation. MS/MS analysis was carried out with an API 3000 mass spectrometer (AB Sciex, Framingham, Massachusetts), and quantitative analysis was performed with ChemoView 1.2 (AB Sciex). The measurements were evaluated using standard values optimized with those established for newborn screening: C0, ≤20 μmol/L; C5, ≥0.6 μmol/L; C5/C0 ratio, ≥0.03.

Results

The clinical features of the 22 patients are shown in the **Table**. The study cohort comprised 15 males and 7 females, ranging in age from 2 months to 42 years (median, 1 year, 11 months). All patients were aged ≥1 year except for a 2-month-old boy who experienced unconsciousness associated with arrhythmias. Ten patients developed symptoms at age 1 year, and 1 boy experienced a convulsion associated with hypoglycemia at age 2 years. Four patients were aged 3 years, and 6 patients were aged ≥4 years. One patient was a 42-year-old woman. Serum C0 values ranged from 0.25 to 19.66 μmol/L (median, 1.31 μmol/L); C5 values, from 0.43 to 11.92 μmol/L (median, 3.23 μmol/L).

Nine patients had known underlying disease. Fourteen patients developed acute encephalopathy, along with convulsions and altered consciousness, 12 of whom had accompanying hypoglycemia. Four patients had hypoglycemia with altered consciousness, without signs of encephalopathy. Myopathy and myalgia were observed in 2 older patients (patients 20 and 22). Hepatic dysfunction was detected in 1 patient (patient 21). Eighteen patients had a previous infectious disease, such as upper respiratory infection, gastroenteritis, or otitis media. Among the remaining 4 patients, a 1-year-old boy developed acute encephalopathy during weaning from breast-feeding, and 2 patients developed encephalopathy after prolonged starvation.

All 22 patients received PCA therapy; data on the administration periods were available for 16 patients. Ten patients received PCAs for >14 days, and 6 patients received PCAs for between 6 and 12 days. In 3 patients, PCAs were given for prophylaxis purposes for >14 days. Patients 5 and 9 developed encephalopathy on day 4 and day 5 after the cessation of PCA therapy, respectively. In 5 patients, PCAs were administered intermittently for periods of several months. Two patients, both aged >3 years, were prescribed valproic acid in addition to PCAs (patients 13 and 19). There was no significant correlation between the duration of PCA treatment and the severity of hypoglycemia or clinical symptoms.

Blood glucose levels were reduced in most patients, except for the 2-month-old boy (patient 1) and 4 older patients (patients 19-22). In 9 of the 14 patients with acute encephalopathy, blood glucose level was <1.3 mmol/L. Blood glucose levels were statistically significantly lower in the patients with acute encephalopathy than in those with hypoglycemia without encephalopathy ($P < .05$). Blood NH_3 levels were elevated in 11 patients with acute encephalopathy, only 3 of these patients (patients 15 [aged 3 years, 8 months], 16 [aged 3 years, 8 months], and 21 [aged 12 years]) had a level >200 μmol/L (normal value, <35 μmol/L). Patient 15 had a C0 level of 0.21 μmol/L and a blood glucose value of 0.17 mmol/L, and patient 16 had a C0 level of 0.91 μmol/L and a blood glucose value of 0.33 mmol/L, all significantly below normal values. No correlation was identified between serum NH_3 and C0 levels.

Serum acylcarnitine analysis confirmed concomitant increases in C5 and decreases in C0 (≤20 μmol/L) in all patients, demonstrating carnitine deficiency. Serum C0 ranged from 0.21 to 19.56 μmol/L, with a median value of 3.23 μmol/L and a mean (SD) value of 6.49 (6.41) μmol/L. There was a marginal correlation between C0 level and blood glucose level, but no correlation between C0 level and clinical symptoms. Among the 10 patients who received PCA treatment for >14 days, 8 had a serum C0 level <5 μmol/L. In contrast, administration of PCAs for <14 days also resulted in reductions in C0 in 4 patients. Among these, a 2-year-old boy (patient 12) experienced convulsions associated with hypoglycemia and a reduction of C0 to 1.37 μmol/L, after 7 days of cefcapene pivoxil and 4 days of cefditoren pivoxil.

Two patients (cases 9 and 12) underwent genetic analysis for *SLC22A5*, the gene responsible for systemic primary carnitine deficiency (CDSP; OMIM #212140); however, no mutation was found in any allele. The clinical courses of the other 20 patients after the discontinuation