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Carnitine-Associated Encephalopathy Caused by Long-term Treatment With an Antibiotic Containing Pivalic Acid

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ABSTRACT

An 18-month-old boy was treated with an antibiotic containing pivalic acid for 6 months for intractable otitis media and then developed repeated convulsions and loss of consciousness. Laboratory data showed hypoglycemia and hypocarnitinemia. Intravenous administration of glucose was ineffective against the seizures and loss of consciousness. However, the patient regained consciousness and recovered soon after intravenous infusion of carnitine. To our knowledge, intravenous carnitine administration that contributed to marked improvements in neurologic deficit caused by administration of an antibiotic containing pivalic acid has not been reported previously. These findings indicate that long-term use of such antibiotics should be avoided.

THE INCIDENCE OF antibiotic-resistant bacteria, such as β-lactamase–negative ampicillin-resistant *Haemophilus influenzae* and penicillin-resistant *Streptococcus pneumoniae*, has continued to rise and results in various health care problems such as the development of refractory infectious diseases and inappropriate administration of antibiotics. Herein, we report the case of an 18-month-old boy who had taken cefditoren pivoxil, a pivalic-acid–containing antibiotic, for ~6 months for intractable otitis media and subsequently developed marked hypoglycemia and carnitine deficiency. This patient showed characteristic clinical manifestations that affected his state of consciousness in association with hypoglycemia and hypocarnitinemia.

CASE REPORT

An 18-month-old boy was referred to Toyohashi Municipal Hospital because of repeated convulsions. The day before the first visit, he developed recurrent vomiting, and his activity and appetite were markedly poor. Six hours before the hospital visit, he became drowsy and was unable to respond to his mother. Generalized tonic seizures, each lasting a few minutes, developed 4 hours later and recurred for almost 2 hours; he then was brought to our emergency department. Eye-opening, verbal responses, and motor response were all scored as 1 on the Glasgow coma scale. Low-grade fever was apparent. No neck stiffness, Kernig sign, or hepatosplenomegaly was seen. His height (80.1 cm) and weight (10.3 kg) were within the reference ranges, and his developmental history was age appropriate. His blood glucose level was only 11 mg/dL. Values of serum transaminases, electrolytes including calcium, and ammonia were all within the reference ranges, and the blood lactate level was also within the reference range (Table 1). Blood gas analysis revealed mild metabolic acidosis, and a urine dipstick test showed an ~5 mg/dL result for ketones. Results of profiles of blood amino acids and urinary organic acids were normal. Cerebrospinal fluid showed normal chemistry and cell counts except for a low glucose concentration of 20 mg/dL. Computed tomography of the brain showed no abnormalities. Initially, disturbance of consciousness and repeated convulsions were assumed to be results of severe hypoglycemia of unknown etiology. A high blood glucose level was seen immediately after intravenous provision of glucose, but it was temporary and quickly corrected to within the

Key Words: carnitine, encephalopathy, hypoglycemia, otitis media, pivalic acid, antibiotics

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TABLE 1 **Laboratory Data From Venous Blood and Glasgow Coma Scale Scores**

	On admission	4 h	8 h	12 h	24 h	48 h
pH	7.365	7.355	7.352	7.405	7.365	7.390
P_{CO_2}, mm Hg	30.6	30.2	22.5	31.0	32.9	28.7
HCO_3^-, mmol/L	17.1	16.4	12.1	19.1	18.4	17.0
Base excess	−6.8	−7.6	−11.8	−4.2	−5.7	−6.5
Lactate, mmol/L	1.2	3.2	5.1	5.7	3.3	4.8
Glucose, mg/dL	11	247	109	128	128	121
Anion gap, mmol/L	18.9	18.6	26.9	13.9	17.6	18
Glasgow coma scale scores	E1, M1, V1	E1, M1, V1	E1, M1, V1	E2, M1, V4	E4, M5, V6	E4, M5, V6
Therapy	IV glucose		Carnitine	DIV →	→	→

P_{CO_2} indicates partial pressure of carbon dioxide; HCO_3^-, hydrogen carbonate ions; E, eye opening; V, verbal response; M, motor response; IV, intravenous; DIV, intravenous drip; →, continuing.

reference range. However, his state of consciousness did not recover, and the seizures did not stop. Seizures were subsequently controlled by diazepam 30 minutes after arrival. Because a clinical diagnosis of encephalitis and/or encephalopathy was made, immunoglobulin, dexamethasone, and acyclovir were administered 5 hours after admission, but this treatment was ineffective. His blood lactate level increased gradually, and metabolic acidosis worsened markedly 4 hours later (Table 1).

Again, we asked the parents about his medical history and found that he had been taking cefditoren pivoxil (prescribed by another clinic) for 6 months to treat intractable otitis media. This information strongly suggested secondary carnitine deficiency. After obtaining written informed consent from his parents, L-carnitine was administered to the patient intravenously at 100 mg/kg per day starting 10 hours after admission. One hour later (Table 1), his acidotic state began to improve, and scores on the Glasgow coma scale increased. Within half a day, the patient could talk with his family as usual. L-carnitine supplementation was continued for another 2 days without any adverse effects such as diarrhea. Supplementation was ceased after confirming that the patient could eat sufficiently.

The patient's serum concentrations of total and free carnitine were 7.4 and 6.2 μmol/L (reference ranges[1] for age: 38.1 ± 11.9 and 30.7 ± 10.3 μmol/L), respectively, at the time of admission and increased rapidly after administering L-carnitine. One month later, his serum concentrations of both total and free carnitine remained within the reference ranges without any carnitine supplementation. At the time of this writing, the patient no longer showed any signs of metabolic disorders and has had a normal acylcarnitine pattern.

DISCUSSION

Carnitine is essential for transportation of long-chain fatty acids into mitochondria and, thus, for fatty acid oxidation. In turn, fatty acid oxidation and ketone-body formation in the liver are essential for energy production in the fasting state.[2] Patients with systemic carnitine deficiency present with episodic vomiting, encephalopathy,[3] cardiomyopathy, and/or Reye-like syndrome.[4]

Pivalic acid combines very efficiently with carnitine in humans to form pivaloylcarnitine, which is excreted in the urine.[5–8] Thus, excessive or prolonged administration of antibiotics that contain pivalic acid (Table 2) may result in secondary carnitine deficiency,[9] particularly in younger children who are less efficient than adults at biosynthesizing carnitine. Indeed, just 1 to 2 weeks of treatment with prodrugs that contain pivalic acid can reduce serum free carnitine concentrations by ~25%.[10] Brass et al[11] have reported that losses of this magnitude are not thought to result in clinically adverse effects. However, 4 pediatric cases of secondary carnitine deficiency that resulted from long-term treatment with antibiotics that contain pivalic acid were reported recently in 1- to 4-year-old children in Japan.[12] These patients received pivalic-acid–containing antibiotics for ~1 to 2 months for treatment of otitis media and/or upper respiratory infection. All the patients showed appetite loss, hypoglycemia of ~11 to 26 mg/dL, loss of consciousness, and convulsions. The level of consciousness in these 4 patients improved soon after correction of the hypoglycemic state.

Our patient had also received an antibiotic containing pivalic acid, cefditoren pivoxil, over a period of ~6 months for treatment of intractable otitis media. As a result of this treatment, the patient developed recurrent convulsions and loss of consciousness in association with severe hypoglycemia and hypocarnitinemia, similar to the cases reported previously. However, adequate correction of his hypoglycemia in this case did not improve the repeated convulsions, disturbance of consciousness, or progressive metabolic acidosis. After glucose infusion, his serum lactate level increased, which suggests that administered glucose was converted to lactate by anaer-

TABLE 2 **Antibiotics That Contain Pivalic Acid**

Generic Term	Abbreviation
Cefditoren pivoxil	CDTR-PI
Cefcapene pivoxil	CFPN-PI
Cefteram pivoxil	CFTM-PI
Pivmecillinam	PMPC
Pivampicillin	PVPC

obic glycolysis because of poor mitochondrial function. The impaired consciousness and associated metabolic acidosis, mainly caused by hyperlactacidemia, were improved after intravenous carnitine supplementation, which suggests that the major pathogenetic mechanism responsible for encephalopathy was a deficit of carnitine metabolism per se, not secondary hypoglycemia. The precise mechanism underlying the efficacy of carnitine administration for impaired consciousness in this case remains unclear. However, substantial differences in the duration of administration were seen between cases. The other patients previously reported had received such antibiotics for ~1 to 2 months at most, whereas our patient had received these antibiotics for as much as ≥6 months, which suggests that depletion of his total-body carnitine store was more excessive than that seen in the other cases. In addition, in some patients with inherited metabolic disorders that are associated with carnitine deficiency, such as fatty acid oxidation, clinical manifestations including neurologic deficit do not always parallel the blood glucose level.[13] A recent experiment in rats showed that L-carnitine administration inhibits hypoglycemia-induced neurologic damage in the hippocampus, presumably by preserving mitochondrial functions.[14] To our knowledge, intravenous carnitine administration that contributed to marked improvements in neurologic deficit caused by administration of an antibiotic containing pivalic acid has not been reported previously. Carnitine is known to be a significant regulator of the intramitochondrial acyl-coenzyme A/coenzyme A ratio, in addition to being essential for mitochondrial fatty acid oxidation.[4,15] A deficit of tissue carnitine leads to mitochondrial dysfunction and an increase in the accumulation of lactate, as noted in the critical phase of our patient despite the lack of signs of suspected peripheral circulatory failure. Ito et al[9] reported that medication with this type of antibiotic may have adverse effects on mitochondrial functions, even in short-term therapy, and advised that carnitine supplementation may be effective for patients who are taking these antibiotics and particularly for those who are vulnerable to carnitine deficiency and/or hyperammonemia, such as patients with organic acidemias, urea-cycle disorders, fatty acid–oxidation defects, or recurrent Reye-like syndromes or those who are receiving valproate or benzoate.

CONCLUSIONS

Antibiotics that contain pivalic acid are widely used in Japan, the United States, and other parts of the world to treat patients with chronic infections, including intractable otitis media and urinary tract infection. Of course, needless administration of antibiotics should be avoided, but for cases in which long-term treatment with these drugs for >2 weeks is required,[9,10] carnitine supplementation is advised.

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