Tohoku J. Exp. Med., 2018, **244**, 279-282

Hypocarnitinemia Observed in an Infant Treated with Short-Term Administration of Antibiotic Containing Pivalic Acid

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Carnitine is a water-soluble amino acid derivative required for β-oxidation of long-chain fatty acids. In carnitine cycle abnormalities and low carnitine states, fatty acid β-oxidation is inhibited during fasting, resulting in hypoglycemia. Pivalic acid is a substance used in prodrugs to increase absorption of parent drugs, and antibiotics containing pivalic acid are frequently used as wide spectrum antibiotics for pediatric patients in Japan. Pivalic acid released after absorption is conjugated with free carnitine to form pivaloylcarnitine, which is then excreted in urine. As a consequence, long-term administration of pivalic acid containing antibiotics has been associated with depletion of free carnitine, inhibition of energy production and subsequent hypoglycemia. Here we report a case of a 23-month-old boy treated with an antibiotic containing pivalic acid for 3 days for upper respiratory tract infection. Laboratory data at referral indicated hypoglycemia, decreased free carnitine and elevated five-carbon acylcarnitine. Isomer separation confirmed the major component of increased five-carbon acylcarnitine to be pivaloylcarnitine, thereby excluding the possibility of a genetic metabolic disorder detected with similar acylcarnitine profile. The level of carnitine was normal when the antibiotic was not administered. Our case shows that the use of antibiotics containing pivalic acid in young children requires consideration of hypocarnitinemia, even with short-term administration.

Keyword: antibiotics containing pivalic acid; hypocarnitinemia; hypoglycemia; isomer separation; pivaloylcarnitine
Tohoku J. Exp. Med., 2018 April, **244** (4), 279-282.

Introduction

Pivalic acid-containing antibiotics are widely used to pediatric patients in Japan. The risk of hypocarnitinemia and subsequent hypoglycemia is associated with the use of this class of antibiotics, although awareness of this association still remains limited. Previous reports have shown that long-term oral administration of pivalic acid-containing antibiotics results in secondary carnitine deficiency and hypoglycemia (Nakajima et al. 2010). There are also reports of hypocarnitinemia induced by short-term administration of these antibiotics to pediatric patients with underlying conditions such as muscular dystrophy (Ito et al. 2017).

Here, we report a case of a previously healthy 23-month-old boy who developed hypocarnitinemia after 3-day-administration of a pivalic acid-containing antibiotic. Elevation of five-carbon acylcarnitine (C5) was observed, 70% of which was confirmed to be pivaloylcarnitine by isomer separation. Free carnitine level in the blood had dropped to one third of his usual free carnitine level. The antibiotic exerted a greater effect on his carnitine level than the poor oral intake, vomitting and diarrhea observed in a subsequent episode of gastroenteritis.

Case Report

A 23-month-old boy developed nasal discharge and cough 7 days prior to admission to our hospital. Three days prior to admission, he also developed a fever of 38°C, and his doctor prescribed cefditoren pivoxil (6 mg/kg/day) for upper respiratory tract infection. Since the patient's dietary intake was decreasing, he was referred to our hospital and admitted for supportive care. On the day of hospitalization, he exhibited fever, progressive dry cough, and a loss of appetite. His previous medical history was unremarkable.

The patient was of normal stature with height of 81.0 cm and weight of 10.1 kg. He was febrile to 37.2°C. His systolic blood pressure was 84 mmHg, pulse 129/min, and respiratory rate 40/min with an O_2 saturation of 99% in room air. Although his glasgow coma scale was 15, he seemed slightly lethargic. There were no rales to auscultation. Hepatomegaly was not recognized. The patient's

Received February 2, 2018; revised and accepted March 23, 2018. Published online April 6, 2018; doi: 10.1620/tjem.244.279.
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liver function tests were normal (AST 50 U/L, ALT 18 U/L). Creatine kinase (CK) was 107 U/L. Plasma glucose level was 38 mg/dL, total ketone bodies were 7,503.3 μmol/L, acetoacetic acid was 2,356.1 μmol/L, and 3-hydroxybutyric acid was 5,147.2 μmol/L. Venous blood gas analysis showed a pH of 7.348, pCO_2 30.1 mmHg, HCO_3^- 16.2 mEq/L, base excess (BE) −8.2 mEq/L, and anion gap 24.8 mmol/L. A rapid respiratory syncytial virus (RSV) antigen test was positive. A chest X-ray was normal. Thus, the patient was diagnosed as having an upper respiratory RSV infection and ketotic hypoglycemia, and he was treated with intravenous injection of 20 ml of 20% glucose solution followed by intravenous fluid administration with glucose infusion rate of 4.9 mg/kg/min. After 1 hour of treatment, the plasma glucose level rose to 116 mg/dL. There was no further lowering of the blood glucose level thereafter, and the patient became active. The patient was discharged on the fifth day after admission.

Carnitine analysis by tandem mass spectrometry of dried blood spot on filter paper taken at the time of hospitalization revealed a reduction in the free carnitine level to 10.8 nmol/mL (normal range > 20 nmol/mL) and an elevation of C5 to 1.4 nmol/mL (cut-off > 1.0 nmol/mL). A d9-isovalerylcarnitine peak, indicative of isovaleric acidemia, a genetic metabolic disorder, was not significant by C5 isomer separation; instead, a pivaloylcarnitine peak was observed, accounting for about 70% of C5 (Fig. 1) (Yamada et al. 2015). Free carnitine clearance was 0.5%, negating a primary carnitine deficiency. Based on these results and his history of taking pivalic acid-containing antibiotic, diagnosis of secondary carnitine deficiency caused by pivalic acid-containing antibiotics was made. Since he was consuming a well-balanced diet after recovery, and the period of antibiotic administration was short, we decided to observe his carnitine level without carnitine supplementation.

Twenty days after discharge, the patient developed gastroenteritis. He exhibited vomiting, diarrhea, and a loss of appetite for 18 hours on the day of hospitalization, but a reduction in the free carnitine level was not observed, at 26.8 nmol/mL. C5 was reduced to normal level at 0.11 nmol/mL. Thirty days after the initial hospitalization, the patient's free carnitine level was 31.3 nmol/mL, and the C5 level was 0.12 nmol/mL (Table 1). The free carnitine level had recovered to normal level from the initial reduction without replacement of oral carnitine.

Discussion

Carnitine is a water-soluble amino acid derivative. In adults, 75% of the required amount of carnitine is obtained from the diet, and the remaining 25% is synthesized from lysine and methionine in the liver and kidney. Carnitine exists in the form of free carnitine and acylcarnitine in the body, and the majority is stored in skeletal muscle. In the kidney, carnitine is excreted in urine after reabsorption of 98% (Stanley 2004). Infants and small children are at increased risk of carnitine depletion because of their lower carnitine synthesis capacity and smaller muscular volume. Carnitine plays a key role in several cellular energy production pathways. For example, it is required for the transportation of long-chain fatty acids across the inner mitochon-

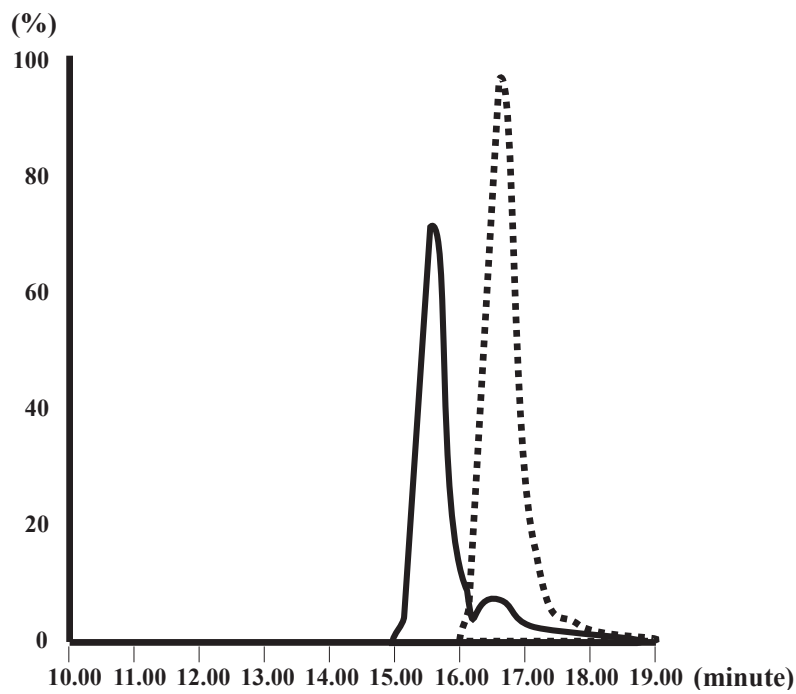

Fig. 1. MS/MS chromatogram of C5 isomers.
Solid line depicting the result of our patient shows a dominant pivaloylcarnitine peak. A d9-isovalerylcarnitine peak which indicates isovaleric acidemia is shown in dotted line for reference.

Table 1. Carnitine analysis data.

Episode	1st[a]	2nd[b]	3rd[c]
C0 (nmol/mL)	10.8	26.8	31.3
C5 (nmol/mL)	1.4	0.11	0.12

C0, free carnitine; C5, five-carbon acylcarnitine.
[a]patient had upper respiratory infection, administration of cefditoren and loss of appetite.
[b]patient had gastroenteritis and loss of appetite.
[c]patient in stable condition.

drial membrane for β-oxidation and production of energy (Robert et al. 2015). In carnitine cycle abnormalities and low carnitine states, fatty acid β-oxidation is inhibited during fasting, resulting in hypoketotic hypoglycemia.

Antibiotics containing pivalic acid are absorbed by the body and broken down into pivalic acid and antibacterial components. Pivalic acid is conjugated with free carnitine in the liver to form pivaloylcarnitine, which is then excreted in the urine. Reflecting the depletion of carnitine in the liver, serum carnitine level decreases, and the risk of hypoglycemia increases with prolonged fasting. Multiple cases of hypocarnitinemia resulting from treatment with antibiotics containing pivalic acid have been reported. In the majority number of cases, antibiotics were administered for more than 1 week (Kobayashi et al. 2016). In one case of hypocarnitinemia following administration of antibiotics for 3 days, the patient had underlying muscle dystrophy (Ito et al. 2017).

A case like our patient, a previously healthy child with no medical concerns or dietary problems, receiving the causative antibiotic for only 3 days before developing hypocarnitinemia, is rare. Our report is also unique in that an elevation of pivaloylcarnitine in the blood was confirmed by isomer separation. The result enabled us to render a quick diagnosis of secondary carnitine deficiency caused by pivalic acid-containing antibiotic.

Carnitine deficiency is characterized by hypoketotic hypoglycemia. In the present case, given the short duration from the initiation of oral antibiotics to hospitalization, tissue carnitine was assumed not to be depleted. Hence, the patient's hypoglycemia was ketotic, reflecting the initiation of β-oxidation by the carnitine remaining in the liver. However, it was apparent that the patient's carnitine level was declining rapidly. Administration of 6 mg/kg/day of cefditoren pivoxil theoretically deprives the body of 0.1 mmol carnitine daily in a 10 kg child. The total carnitine pool has been estimated to be 10-15 mmol for children aged 2-9.5 years (Holme et al. 1992). Had antibiotic treatment not been discontinued and the child's dietary intake had continued to decline, carnitine depletion in the tissue would have followed shortly, resulting in the inhibition of β-oxidation and severe hypoketotic hypoglycemia. Moreover, although some studies have reported that the short-term administration of pivalic acid-containing antibiotics is safe (Brass 2002), and that only long-term administration causes adverse events (Nakajima et al. 2010), several days of antibiotic administration was shown to cause blunted ketogenesis in some patients (Abrahamsson et al. 1994), as well as elevated levels of ammonia, suggesting an adverse effect of liver carnitine depletion on mitochondrial function (Ito et al. 1995).

One might suspect that the patient had "ketotic hypoglycemia," a disease characterized by recurrent episodes of hypoglycemia with ketosis. It was a possibility that the patient was experiencing his first episode of many more episodes of ketotic hypoglycemia to come. However, we denied his suffering from the disease because he has not presented with another episode of hypoglycemia with ketosis thereafter. Even when the patient developed gastroenteritis, exhibited vomiting, diarrhea, and a loss of appetite for 18 hours, he did not develop hypoglycemia with severe ketosis.

Lastly, this patient was eventually diagnosed as having an upper respiratory RSV infection, meaning that the administration of cefditoren pivoxil was not indicated. Pivalic acid-containing antibiotics, including cefditoren pivoxil, are widely used to pediatric population in Japan. The use of these antibiotics should be limited to cases where they are truly necessary, including infections with resistant strains of bacteria. Where their use is mandated, increased attention to the risk of hypocarnitinemia is required, even with short-term administration to a previously healthy child.

Acknowledgments

We thank Clare Cox, Ph.D., from Edanz Group (https://www.edanzediting.com/ac) for editing a draft of this manuscript.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare no conflict of interest.

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