Carnitine-related hypoglycemia caused by 3 days of pivalate antibiotic therapy in a patient with severe muscular dystrophy: a case report

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Abstract

Background: Long-term treatment with antibiotics containing pivalic acid may decrease serum carnitine concentration and can sometimes be associated with severe hypoglycemia and encephalopathy in infants. Little has been reported, however, on severe hypocarnitinemia induced by acute administration in older children.

Case presentation: We describe a 6-year-old Japanese girl with Fukuyama-type congenital muscular dystrophy who lost consciousness after 3 days of treatment with an antibiotic containing pivalic acid (cefditoren pivoxil). Investigations at the onset of unconsciousness revealed hypoglycemia (free plasma glucose concentration: 31 mg/dL) and hypocarnitinemia (serum free carnitine concentration: 6.2 μmol/L). Intravenous administration of glucose rapidly improved her symptoms without any complications. Serum free carnitine concentration was 29.0 μmol/L immediately prior to the initiation of cefditoren pivoxil. Computed tomography scanning showed severe peripheral skeletal muscle atrophy, indicating the likelihood of decreased carnitine stores in skeletal muscle.

Conclusions: Although serum carnitine concentration can appear deceptively normal, skeletal muscle carnitine stores can be reduced in patients with severe muscular atrophy. Even a short course of a pivalate-containing antibiotic can lead to life-threatening hypocarnitinemia in older children with severe muscular dystrophy.

Keywords: Carnitine, Fukuyama-type congenital muscular dystrophy, Antibiotics, Pivalic acid, Hypoglycemia

Background

Carnitine, a water-soluble quaternary amine, is responsible for the intracellular transport of long-chain fatty acids into mitochondria, facilitating fatty acid oxidation. Severe carnitine deficiency impairs β-oxidation, and thereby the ability to produce glucose, which may result in hypoglycemia. Although most patients with carnitine deficiency are asymptomatic, it can cause muscle weakness, hypotonia, nausea and vomiting, fatigue, recurrent infection, failure to thrive, poor appetite, poor concentration, apathy, and headaches. Furthermore, carnitine deficiency can occasionally cause severe and life-threatening complications, including hypoglycemic encephalopathy and dilated cardiomyopathy [1, 2].

Carnitine deficiency may be classified as primary or secondary; the primary form is associated with genetically determined metabolic errors whereas the secondary form is associated with acquired diseases or iatrogenic factors such as drug administration. Recent studies have reported that severe secondary carnitine deficiency induced by long-term administration of pivalate-containing antibiotics, particularly for more than 14 days, causes hypoketotic hypoglycemia and acute encephalopathy in infants [3–6]. However, there have been few reports to date of carnitine deficiency provoked by short-term antibiotics in older children. Here, we report the case of a 6-year-old girl with Fukuyama-type congenital muscular dystrophy (FCMD) who developed...
severe hypoglycemia caused by carnitine deficiency after a 3-day oral course of cefditoren pivoxil (CDTR-PI), an antibiotic containing pivalic acid.

**Case presentation**
A 6-year-old Japanese girl with FCMD was admitted to our hospital with sudden-onset impaired consciousness. She had been diagnosed with FCMD by genetic testing at 9 months of age, having a homo-retrotransposon insertion mutation of the *fukutin* gene. Her height was 108 cm (−1.0 SD) and weight was 13.0 kg (−2.0 SD). She was able to sit but not stand, and could eat only a soft diet. Her Gross Motor Function Classification System score was level five [7]. She had previously been admitted to hospital for treatment of acute pharyngitis, for which she was prescribed CDTR-PI (8.5 mg/kg/day orally). During this time, she could consume half of her usual calorific intake without weight loss or dehydration. After 3 days of treatment, her level of consciousness declined. On physical examination, her Glasgow Coma Scale score was 9 out of 15 (E3V2M4), core temperature was 36.6 °C, blood pressure was 108/68 mmHg, and heart rate was 130 beats/min. Laboratory investigations revealed a serum creatine kinase concentration of 36.6 °C, blood pressure was 108/68 mmHg, and heart rate was 130 beats/min. Laboratory investigations revealed a serum creatine kinase concentration of 588 IU/L and hypoglycemia (free plasma glucose concentration of 31 mg/dL). Hepatic and renal function, serum electrolyte and ammonia concentrations, and acid-base balance were all within the normal range, but serum free carnitine concentration was markedly reduced (6.2 μmol/L) (Table 1).

We diagnosed the patient with hypoglycemia originating from a carnitine deficiency induced by CDTR-PI, as the serum free carnitine concentration was 29.0 μmol/L when measured retrospectively in a sample taken 3 days before CDTR-PI treatment was initiated. The patient was immediately administered intravenous glucose and her level of consciousness rapidly improved without any complications. We discontinued CDTR-PI treatment and initiated L-carnitine supplementation. One month later, the patient's serum free carnitine concentration lay within the normal range with no relapse of symptoms, hypoglycemia, or side effects reported (Fig. 1a).

Computed tomography (CT) scanning undertaken to evaluate skeletal muscle volume showed severe atrophy of the peripheral muscles compared with an age-matched healthy child who had undergone CT to investigate left leg pain (Fig. 1b). We also calculated the renal reabsorption rate of free carnitine (RRFC) using the following equation: RRFC (%) = 1 - (urine free carnitine × serum creatinine)/(serum free carnitine × urine creatinine). An RRFC of 98% (normal value: >95%) indicated that renal carnitine malabsorption was not responsible for the patient’s episode of hypocarnitinemia [8]. Serum creatinine concentration was <0.1 mg/dL in this case; therefore, we substituted 0.1 mg/dL and considered that the true RRFC value must have been above 98%.

**Discussion**
Our patient suffered severe carnitine deficiency induced by 3-day oral administration of CDTR-PI. Pivalic acid is released as a result of the metabolism of the prodrug CDTR-PI, and combines with serum free carnitine to form pivaloylcarnitine, which is excreted by the kidneys. Consequently, long-term treatment with an antibiotic containing pivalic acid may provoke hypocarnitinemia [3–6, 9], especially in patients at risk of carnitine deficiency such as those with inherited causes of carnitine metabolism, severe epilepsy, renal disorders or severe neurologic disability, infants less than 2 years old, and patients fed parenterally or taking multiple antiepileptic drugs [10, 11]. However, a case has been reported of a 1-year-old Japanese patient with hypoglycemia associated with hypocarnitinemia in-duced by 2 days of cefcapene pivoxil treatment [12]. Additionally, Ito et al. reported that treatment with cefteram pivoxil significantly decreased the level of serum free carnitine in both children and adults, even

### Table 1 Blood examination, chest X-ray, and echocardiographic findings on admission

| Hematological examination | Biochemistry | Blood gas (vein) |
|---------------------------|--------------|-----------------|
| Hemoglobin (Hb) 12.9 g/dL | AST 65 U/l | pO2 46.4 mmHg |
| Red Blood Cells (RBC) 3.5 × 106/μl | ALT 38 U/l | pCO2 39.9 mmHg |
| Platelets (Plt) 38.9 × 105/μl | Na 135 mEq/l | Lac 9.0 mmol/l |
| White Blood Cells (WBC) 1.8 × 103/μl | K 4.2 mEq/l | BE 1.8 mmol/l |
| Neutrophils (TP) 7.1 g/dl | Cl 97 mEq/l | |
| Creatinine <0.10 mg/dl | Serum creatinine (just 3 days before cefditoren pivoxil was started) |
| Total Carnitine 14.1 μmol/l | Total Carnitine 33.7 μmol/l |
| Free Carnitine 6.2 μmol/l | Free Carnitine 29.0 μmol/l |
| Acyl Carnitine 4.7 μmol/l | Acyl Carnitine 7.9 μmol/l |
| Chest X-ray | Echocardiographic study |
| Cardiothoracic ratio 50% | IVC diameter 11 mm |
| Lungs | normal | Caval/Ao ratio 0.9 (normal value: 0.8–1.0) |
in short-term therapy, and advised that carnitine supple-
mentation may be necessary for patients who are tak-
ing these antibiotics, particularly those vulnera-
table to carnitine deficiency [13]. Although our patient
was an older child who could usually receive adequate
 calories orally (1200 kcal/day, appropriate for her
body weight and activity level), she did not receive
enough to eat for 3 days (about half of her usual
calorific intake) after antibiotic treatment was initiated
because of her acute pharyngitis.

We judge, however, that even if our patient’s diet had
been marginally deficient in carnitine, her most impor-
tant risk factor for carnitine deficiency was severe muscu-
lar dystrophy. Large quantities of carnitine can be stored
in skeletal muscle; in a healthy patient, the proportion
stored in skeletal muscle exceeds 95% [1]. Consequently,
severe muscle atrophy such as that seen in patients with
Duchenne or Becker muscular dystrophy [14, 15] re-
duces the capacity to store carnitine and replenish
serum free carnitine when it is suddenly depleted, even
when the renal reabsorption of carnitine is normal. As
far as we are aware, there have been no previous reports
of carnitine deficiency in FCMD, but our patient’s skel-
etal muscle volume was markedly lower than that of a
healthy child. We suggest that the patient’s reduced
muscle bulk would have further predisposed her to
hypoglycemia, which was likely to the result of a lack of
glycogen and glycogenic amino acid storage in skeletal
muscle as well as β-oxidation impairment. Fever would
also have induced a hypercatabolic state that would have
markedly elevated glucose consumption.

We did not measure blood and urine ketone bodies, a
diagnostic limitation for hypoketotic hypoglycemia in
this patient, because we imitated prompt emergency
treatment for severe hypoglycemia to prevent permanent
central nervous system damage. However, the normal ven-
ous blood gas test results arguably preclude the possibility
of ketotic hypoglycemia. Early diagnosis and rapid, appro-
priate treatment for severe hypoglycemia resolved our
patient’s symptoms without any complications.

The rapid fall in serum free carnitine from 29.0 μmol/
L to 6.2 μmol/L observed in this girl with FCMD after
just 3 days of treatment with CDTR-PI underlines the
speed at which potentially life-threatening symptoms
can develop in patients at risk of carnitine deficiency. It
is important to note that pivalate antibiotics are not the
only type of antibiotic that can influence serum free car-
nitine; β-lactam antibiotics are reported to competitively
block the binding of organic cation/carnitine trans-
porter 2 (OCTN2) and inhibit reabsorption in the
kidney [16, 17]. As far as we are aware, however,
there have been no reports of β-lactam antibiotics causing
adverse events such as those seen in this case.

Conclusions

This case shows that even short-term administration of
antibiotics containing pivalic acid in older children with
severe musculoskeletal disorders requires careful moni-
toring for carnitine deficiency to avoid serious adverse
effects. Alternative antibiotics should therefore be
administered to children at risk. Supplementation with
L-carnitine is recommended so that complications can
be avoided if alternative antibiotics cannot be identified.

Abbreviations

CDTR-PI: Cefditoren pivoxil; CT: Computed tomography; FCMD: Fukuyama-
type congenital muscular dystrophy; OCTN2: Organic cation/carnitine
transporter 2; RRFC: Renal reabsorption rate of free carnitine
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Availability of data and materials
The data from this study are available from the corresponding author upon requests.

Authors’ contributions
MI and YS provided the emergency report for the patient at the outpatient clinic and wrote the manuscript. MF performed the medical care and wrote and revised the manuscript. HW and B both helped with the acquisition of data, data analysis and interpretation, and critical review of the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Written informed consent was obtained from the patient’s parents for the publication of this case report, images, and all information contained in it.

Ethics approval and consent to participate
All examinations and investigations in this case were approved by the ethics committee of Ehime University Graduate School of Medicine. Written informed consent was obtained from the parents of the patient for publication of this case report and any accompanying images.

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