PMDA Alert for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency

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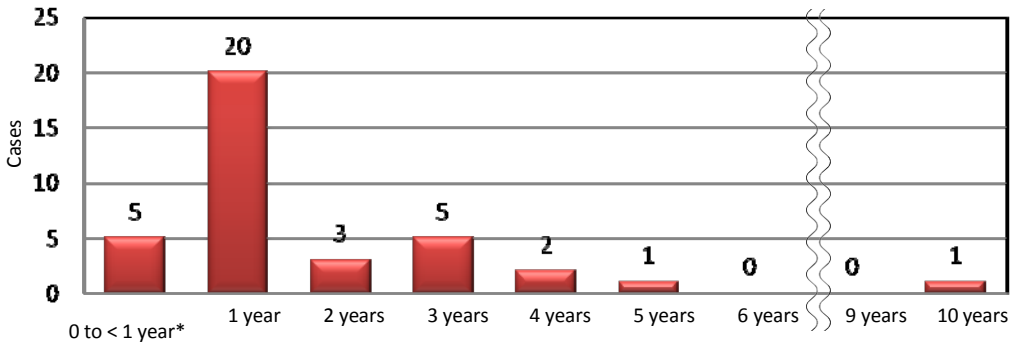
This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail

Serious hypocarnitinemia and hypoglycaemia in children treated with antibacterials with a pivoxil group

Antimicrobials with a pivoxil group (see page 4) are widely used for the treatment of infections such as otitis media. However, in administrating to children, hypoglycaemia, convulsion, and encephalopathy, etc. associated with serious hypocarnitinemia have been reported, resulting in sequel in some cases.
Use of antibacterials with a pivoxil group may increase carnitine excretion, leading to hypocarnitinemia. The following precautions should be taken in children, especially in infants, since their blood carnitine level is low.

- Children (especially infants) treated with antibacterials with a pivoxil group should be monitored for hypoglycemic symptoms (e.g., decreased level of consciousness and convulsion) associated with decreased blood carnitine levels. (See Figure: Distribution of age at the onset of adverse reactions)
- In some reports, hypoglycaemia associated with hypocarnitinemia occurred on the day following treatment, not only in case of long term treatment. (See Case 3)
- Hypocarnitinemia may occur in neonates of mothers treated with antibacterials with a pivoxil group during her pregnancy. (See Case 4)

Figure: Distribution of age at the onset of adverse reactions



* Including 1 case of hypocarnitinemia in mother who treated with an antibiacterial with a pivoxil group during her pregnancy, resulting in hypocarnitinemia in a baby. (See Case 4 on page 3)

Table: Hypocarnitinemia and hypoglycaemia reported as adverse reactions
(Based on company reports and published literature as of January 31, 2012)

Item	Number of cases
All	38*
With sequela	3
Duration of treatment (time to onset)	
< 14 days	9**
≥ 14 days	27
Unknown	2
Food intake	
Poor	16
Good	5
Unknown	17
Symptoms of adverse drug reactions	
Hypoglycaemia	31
Convulsion and tremor (including jitteriness and extremity stiffness)	24

*The mother in Case 4 on page 3 is included.
**The shortest time to onset was 2 days (the next day of treatment).

Mechanism of hypocarnitinemia and hypoglycaemia[1)2)]

Antibacterials with a pivoxil group contain pivalic acid ester-linked to the active ingredient to promote gastrointestinal absorption. Once absorbed, the drug is metabolized into pivalic acid and the active substance. After conjugation with carnitine, pivalic acid turns into pivaroyl carnitine, which is excreted in urine. As a result, it is known that serum carnitine decreases.

Carnitine is taken in food as well as supplied by biosynthesis of amino acid. It is required for fatty acid beta oxidation in the mitochondria, which usually provide energy for gluconeogenesis in a fasting or starving state. Lack of carnitine prevents fatty acid beta oxidation and gluconeogenesis, causing hypoglycaemia.

1): Melegh B,et al. Biochem Pharmacol. 1987; 36: 3405-3409.
2): Holme E, et al. Lancet. 1989; 2(8661): 469-473

Case summaries

Case 1

1-year-old male patient; weight, 12 kg; acute otitis media; medical history, pulmonary artery stenosis

The patient started receiving 150 mg (potency)/day of cefditoren pivoxil for the treatment of bilateral acute otitis media. The dose was increased to 200 mg (potency)/day because the symptoms did not improve. At approximately 4 months of treatment (2 days after the dose increase), **generalized tetanic spasms** occurred even though **the patient had dinner as usual the day before.** The examination showed decreased blood glucose (21 mg/dL), decreased blood carnitine, **convulsion, decreased level of consciousness (Japan Coma Scale [JCS]: 100),** and **brain oedema**. Glucose (intravenous infusion), a carnitine preparation, diazepam, and mannitol were administered. His level of consciousness improved on Day 4 of onset. However, the patient **was left with paralysis on the left side and epileptic seizures**. Administration of antiepileptics was started and continued for approximately 2 years. The paralysis eventually improved. The patient has had no epileptic seizure since.

Case 2

0-year-old male patient; weight, 9 kg; pharyngitis

The patient had intermittently received cefditoren pivoxil and cefcapene pivoxil for the treatment of common cold for approximately 4 months (cefditoren pivoxil for 28 days in total and cefcapene pivoxil for 28 days in total). The patient seemed lifeless and was taken to a nearby cliniceven though **he was fed as usual the day before**. **Blood glucose was 11 mg/dL**. Hypocarnitinemia was noted. The patient had a **convulsion** associated with hypoglycaemia during the consultation. After receiving intravenous infusion of glucose, the patient was admitted to the hospital. He recovered on Day 5 of

Case 3

1-year-old male patient; weight, 12 kg; asthma

The patient started receiving 100 mg (potency)/day of cefcapene pivoxil for the treatment of asthmatic bronchitis. His food consumption decreased associated with pyrexia. Since the patient frequently had jitteriness and was restless **on the next day of the day of administration**, he was taken to the hospital on the following day. **The patient still had jitteriness and vomited**. The laboratory tests revealed hypoglycaemia (45 mg/dL) and hypocarnitinemia. After treatment with intravenous infusion of glucose and diazepam, the patient recovered on the same day.

Case 4

Mother in her 20s with pyelonephritis; male neonate with birthweight of 2898 g

The mother started receiving 300 mg (potency)/day of cefcapene pivoxil **in 27 weeks of gestation** for the treatment of pyelonephritis. She had labor pain in 39 weeks and was admitted to the hospital. Administration of cefcapene pivoxil was discontinued. The baby was delivered normally through the vagina and diagnosed with hypocarnitinemia based on the mass screening for inborn errors of metabolism. The mother was also diagnosed with hypocarnitinemia by clinical tests. The mother and the baby were treated with carnitine. The carnitine level became normal at 1 month. No symptoms were noted in either the mother or the baby.

Related information

"Alerts against the use of secondary carnitine deficiency associated with antibacterials with a pivoxil group" is posted in the Journal of the Japan Pediatric Society. (116 (4); 804-806, 2012) Japanese text only

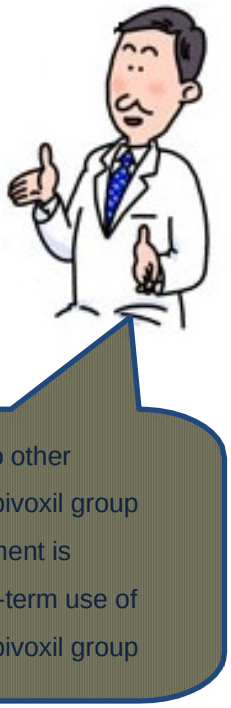
See information on the precautions related to antibacterials with a pivoxil group (provisional translation), at the Pharmaceuticals and Medical Devices Information website
http://www.info.pmda.go.jp/psearch/html/menu_tenpu_base.html (In Japanese)

Product names of antibacterials with a pivoxil group (Name of Marketing Authorization Holder)

Cefcapene Pivoxil Hydrochloride Hydrate
- Flomox Tablet 75 mg, 100 mg, Flomox Fine Granule for Pediatric 100 mg (Shionogi & Co., Ltd.)
- CEFCAPENE PIVOXIL HYDROCHLORIDE Tablet 75 mg “Sawai”, 100 mg “Sawai”, CEFCAPENE PIVOXIL HYDROCHLORIDE Fine Granule for Pediatric 10% “Sawai” (Sawai Pharmaceutical Co., Ltd.)
- CEFCAPENE PIVOXIL HYDROCHLORIDE TABLETS 75 mg “TOWA”, 100mg “TOWA” (CHO Shinyaku Co., Ltd.)
- CEFCAPENE PIVOXIL HYDROCHLORIDE Tablets 75 mg “TCK”, 100 mg “TCK”, CEFCAPENE PIVOXIL HYDROCHLORIDE Fine Granules for Children 100 mg “TCK” (Tatsumi Kagaku co., Ltd.)
- CEFCAPENE PIVOXIL HYDROCHLORIDE Tab. 75 mg “CH”, 100 mg “CH”, CEFCAPENE PIVOXIL HYDROCHLORIDE F.G. 10% ”CH” FOR PEDIATRIC (Choseido Pharmaceutical Co., Ltd.)
- CEFCAPENE PIVOXIL HYDROCHLORIDE FINE GRANULES FOR PEDIATRIC 10% “TOWA” (Towa Pharmaceutical Co., Ltd.)
- Cefcapene Pivoxil Hydrochloride Tablet 75 mg “Nichi-iko”, 100 mg “Nichi-iko”, Cefcapene Pivoxil Hydrochloride Fine Granule 10% for Pediatric “Nichi-iko” (Nichi-Iko Pharmaceutical Co., Ltd.)
- Cefcapene Pivoxil Hydrochloride Fine Granules for Pediatric 10% “JG” (Nihon Generic Co., Ltd.)
- Cefcapene Pivoxil Hydrochloride Tab. 75 mg "Mylan", 100 mg "Mylan", Cefcapene Pivoxil Hydrochloride Fine Granules for Pediatric 10% "Mylan" (Mylan Seiyaku Ltd.)
- CEFCAPENE PIVOXIL HYDROCHLORIDE TABLETS 75 mg “YD”, 100 mg “YD”, CEFCAPENE PIVOXIL HYDROCHLORIDE FINE GRANULES 10% for PEDIATRIC “YD” (Yoshindo Inc.)

Cefditoren Pivoxil
- MEIACT MS TABLETS 100 mg, MEIACT MS FINE GRANULES 10% for Pediatric (Meiji Seika Pharma Co., Ltd.)
- CEFDITOREN PIVOXIL Fine Granule for Pediatric 10% “Taiyo” (Teva Pharma Japan Inc.)
- CEFDITOREN PIVOXIL Tablet 100 mg “Sawai”, CEFDITOREN PIVOXIL Fine Granule for Pediatric 10% “Sawai” (Sawai Pharmaceutical Co., Ltd.)
- CEFDITOREN PIVOXIL Tab. 100 mg “CH”, CEFDITOREN PIVOXIL F.G. 10% “CH” FOR PEDIATRIC (Choseido Pharmaceutical Co., Ltd.)
- CEFDITOREN PIVOXIL TABLETS 100 mg “TOWA”, CEFDITOREN PIVOXIL FINE GRANULES FOR PEDIATRIC 10% “TOWA” (Towa Pharmaceutical Co., Ltd.)
- Cefditoren Pivoxil Tablet 100 mg “Nichi-iko”, Cefditoren Pivoxil Fine Granule 10% for Pediatric “Nichi-iko” (Nichi-Iko Pharmaceutical Co., Ltd.)
- Cefditoren Pivoxil fine granules 10% ”EMEC” for children (Medisa Shinyaku Inc.)

Cefteram Pivoxil
- TOMIRON tablet 50, 100, TOMIRON fine granules 10% for pediatric (Toyama Chemical Co., Ltd)
- CETLAT Tablet 100 mg, CETLAT Fine Granule for Pediatric 10% (Sawai Pharmaceutical Co., Ltd.)
- SOMATRON Fine Granule for Pediatric 100 (Teva Pharma Japan Inc.)
- TERAMIRON FINE GRANULES FOR PEDIATRIC 10% (Towa Pharmaceutical Co., Ltd.)
- Teracefron Fine Granule 100 mg for Pediatric (Nichi-Iko Pharmaceutical Co., Ltd.)



Tebipenem Povoxil
- ORAPENEM FINE GRANULES 10% FOR PEDIATRIC (Meiji Seika Pharma Co., Ltd.)

Pivmecillinam Hydrochloride
MELYSIN TABLETS 50 mg (Takeda Pharmaceutical Company Limited)

About this information

* "PMDA Alert for Proper Use of Drugs" communicates to healthcare providers with clear information from the perspective of promoting the proper use of drugs. The information presented here includes such cases where the reporting frequencies of similar reports have not decreased despite relevant alerts provided in package inserts, among Adverse Drug Reaction/infection cases reported in accordance with the Pharmaceutical Affairs Law.
* We have tried to ensure the accuracy of this information at the time of its compilation but do not guarantee its accuracy in the future.
* This information is not intended to impose constraints on the discretion of healthcare professionals or to impose obligations and responsibilities on them, but is provided to promote the proper use of drugs.

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