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Report

Disproportionality Analysis of Pivalate-Conjugating Antibiotic-Associated Hypocarnitinemia Using the Japanese Adverse Drug Event Report Database

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Background: Pivalate-conjugated *β*-lactam antibiotics (PCAs) have been developed to enhance bioavailability by incorporating the pivoxil group into the *β*-lactam chemical structure. Although there are only case reports and observational studies limited to pediatric patients on PCA-associated hypocarnitinemia, no comparisons have been made across all age groups, and comprehensive data from larger-scale studies are limited. Therefore, we investigated the association between PCA use and the onset of hypocarnitinemia for all age groups by analyzing the Japanese Adverse Drug Event Report (JADER) database. Methods: We analyzed 2,226,010 adverse event cases from the JADER database between April 2004 and March 2024. To detect signals of hypocarnitinemia, we calculated the reporting odds ratio and 95% confidence interval. Results: Among the total reported cases of hypocarnitinemia, the highest number of occurrences (252 cases) and the signal of hypocarnitinemia were detected in PCAs, whereas no cases were observed for other *β*-lactam antibiotics (non-PCAs). Multiple logistic regression analysis revealed that the PCA use, age (< 10 years), and concomitant use of valproate were associated with the onset of hypocarnitinemia. Most patients with hypocarnitinemia were under 10 years of age. An evaluation based on consumption data analysis from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) open database suggested that antimicrobial consumption is highest among children under 10 years of age. Conclusions: Our findings suggest that the use of *β*-lactam antibiotics containing a pivoxil moiety is disproportionately associated with reports of hypocarnitinemia in the JADER database. These findings should be interpreted as hypothesis-generating.

Key words pivalate-conjugated antibiotics, hypocarnitinemia, Japanese adverse drug event report

INTRODUCTION

Carnitine, a low-weight molecule involved in lipid metabolism, plays an essential role in energy production by transporting long-chain fatty acids into the mitochondria.[1-4] In patients with hypocarnitinemia, reduced serum carnitine levels can lead to inhibition of fatty acid beta-oxidation during fasting, resulting in hypoglycemia.[2]

Pivalate-conjugated *β*-lactam antibiotics (PCAs) such as cefcapene pivoxil (CFPN-PI), cefditren pivoxil (CDTR-PI), cefteram pivoxil (CFTM-PI), and tebipenem pivoxil (TBPM-PI), which have pivoxil groups in their chemical structures, have been used to treat bacterial infections in Japan. Owing to its low absorption rate in the intestine, pivalic acid is often conjugated to improve its bioavailability.[3,4] Following absorption, the conjugated pivalic acid is liberated from antibiotics, reacts with endogenous carnitine in the liver, and is excreted in urine in the form of pivaloyl carnitine, resulting in a corresponding deficiency of the concentration of carnitine in serum.[5-8]

In April 2012, the Japan Pediatric Society and the Pharmaceutical and Medical Device Agency (PMDA) warned against the development of severe hypocarnitinemia and subsequent hypoglycemia due to PCA administration and recommended minimizing prolonged misuse and overuse of this class of antibiotics.[9]

Several case reports[10-12] or case series[1,8] have suggested an association between PCA administration and the development of hypocarnitinemia. However, reports on analyses based on a large number of cases and statistically derived evidence, such as patient background involved in the development, time-to-onset, or frequency of this adverse event (AE), remain limited.

Interestingly, hypocarnitinemia, which is associated with severe complications, such as hypoglycemia,[13] coma, and

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encephalopathy,[11,14] does not frequently develop; therefore, previous studies may not have sufficient power to assess the association of PCA use with the onset of hypocarnitinemia. Because hypocarnitinemia is a rare adverse event and large-scale prospective studies are difficult to conduct, disproportionality analysis using spontaneous reporting databases represents a useful pharmacovigilance approach for signal detection. To address this issue, we used the Japanese Adverse Drug Event Report (JADER) database, a large, spontaneous reporting system that contains aggregated AEs managed by the PMDA.

Previous reports have shown that these AEs occur not only in patients receiving long-term therapy but also in those who receive PCAs within a few days;[9,12] detailed analyses of the association between the duration of PCA treatment and the development of hypocarnitinemia are lacking. In addition, there are limited reports on whether the development of hypocarnitinaemia can be attributed to the chemical structure of PCAs among *β*-lactam antibiotics. Previous database studies investigating PCA-associated hypocarnitinemia were conducted primarily in pediatric populations and included a limited number of events.[13,15] Because hypocarnitinemia is a rare adverse event and serum carnitine concentrations are not routinely measured in clinical practice, obtaining sufficient numbers of cases for analysis using conventional healthcare databases is challenging. Spontaneous reporting databases are particularly useful for the pharmacovigilance assessment of rare adverse drug reactions such as hypocarnitinemia. Therefore, we used the Japanese Adverse Drug Event Report (JADER) database to evaluate reporting patterns of PCA-associated hypocarnitinemia and to identify patient characteristics associated with its reporting.

To clarify the association between the development of hypocarnitimemia and the pivoxil structure, this study aimed to use JADER to extract additional information regarding patient-related conditions associated with the onset of hypocarnitinemia.

METHODS

Acquisition, Preprocessing, and Data Creation from JADER The JADER database contains information on spontaneously reported AEs in Japan, and consists of four tables: DEMO (patient demographic information such as sex, age, and body weight), DRUG (information on drug names and causal relationships), REAC (information on AEs and outcomes of patients), and HIST (primary disease information). Data from the four tables were downloaded from the PMDA, and data from April 2004 to March 2024 were included in the analysis.[16]

In the JADER data, the recorded patient data are anonymized; therefore, approval from the Institutional Ethics Review Committee was not required. The data from four tables were merged based on the patient ID numbers (Full data table, Fig. 1). After removing the duplicate entries in the "patient ID number," "participation of drug," "drug name," and "AE" in the Full data table, we obtained the "Primary Dataset" (Fig. 1). Only reports on "suspected drugs" were extracted from the dataset. Dataset A was created after excluding reports with inconsistent time series and those receiving sulfonylureas, short-acting insulin secretagogues, and insulin derivatives (since these drugs can cause hypoglycemia directly or indirectly via the insulin receptor) (Fig. 1).

Definitions of AEs and Drugs Hypocarnitinemia was defined as the target AE. In the REAC table, the names of AEs were extracted according to the Medical Dictionary for Regulatory Activities/Japanese version 27.1 (MedDRA/J),[17] in which the preferred terms (PTs) were used. The PTs used in this study were as follows: "carnitine decreased (PT code:10007668)" and "hypocarnitinemia (PT code:10073952)".

PCAs, non-PCA oral *β*-lactams, adefovir (an antiviral agent containing two pivoxil groups in its chemical structure), and valproate (VPA; an antiepileptic agent; known to induce carnitine deficiency[4]) were employed for the signal detection analysis (Table 1).

Non-PCA oral *β*-lactams that do not have a pivoxil group, such as cefpodoxime, cefuroxime, cefaclor, cefdinir, cefixime, cefroxadine, cephalexin, and faropenem, were included as comparative controls.

Statistical Analysis All analyses were performed using JMP Pro ver. 17.0.0 (SAS Institute Inc., Cary, NC, USA). The reporting odds ratio (ROR), 95% confidence interval (CI), and p-value were employed to estimate the causality between drugs and AEs. p-value < 0.05 was considered statistically significant.

For univariate analysis, a crude ROR was calculated using the following formula with two-by-two contingency tables:

$$\mathrm{ROR} = (a/c)/(b/\mathrm{d}) = ad/bc$$

where a is the number of reports of the target AE with the target drug, b is the number of reports of all other AEs with the target drug, c is the number of reports of the target AE with all the other drugs, and d is the number of reports of all other AEs with all the other drugs.[18] If the number of cases exceeded 3 and the lower limits of the 95%CI for the ROR exceeded 1 (with its corresponding p-value < 0.05), it was judged as a signal.

Univariate and Multivariate Analyses Univariate and multivariate logistic analysis using Dataset A (Fig. 1) were performed to identify independent factors for the onset of hypocarnitinemia. All independent variables were assigned to binary response age (< 10 or ≥ 10 years), PCA user (yes or no), sex (male or female), and concomitant use of medication (concomitant use with or without VPA). The "age" was set as a variable based on the alert issued by PMDA in April 2012[9] regarding the use of PCAs and the development of hypocarnitinemia, whereas the sex of the patients was based on the previous report.[3]

Analysis of the Onset of PCA-Associated Hypocarnitinemia per Prescription To evaluate the onset of hypocarnitinemia per antibiotic prescription, we employed another database, the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB).[19] The NDB, managed by the Ministry of Health, Labor, and Welfare (MHLW), is a health insurance claims database containing most of the available data in the National Healthcare Insurance System in Japan. Recently, MHLW released "NDB open data," a comprehensive compilation of statistics from the Japanese healthcare system that is freely accessible. The NDB open data file, downloaded on October 7, 2025, was employed to analyze antibiotic consumption in the present study to estimate the frequency of hypocarnitinemia. For the age groups ≥ 20 years, the defined daily doses (DDDs) of CFPN-PI, CDTR-PI,

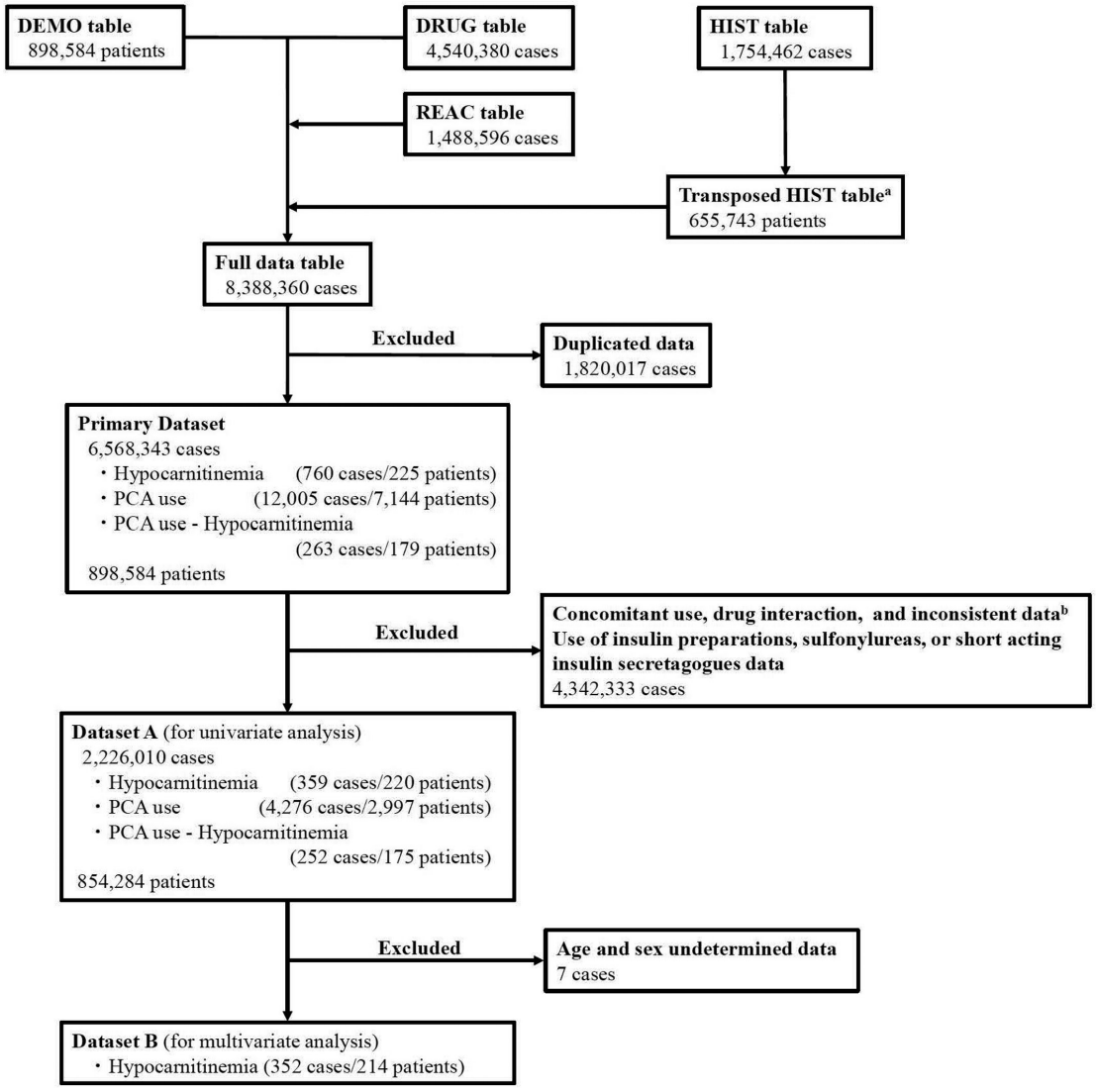

Fig. 1. Flowchart for the Preprocessing and Creation of the Study Cohort Dataset for Analysis Using JADER

In the JADER dataset, the causes of drug-related hypocarnitinemia were divided into three categories: "suspected drugs", "concomitant drugs", and "interaction drugs". Only the data from "suspected drug" was extracted. [a] In the HIST table, information on multiple underlying diseases in a single patient is represented across multiple rows. To simplify the process, information on multiple diseases in one patient was consolidated into a single row in the "Transposed HIST table." [b] If the "date of AEs onset" preceded the "date of start administration," the relevant data were excluded from the analysis.

CFTM-PI, TBPM-PI, and pivmecillinam (PMPC) in the anatomical therapeutic chemical (ATC)/DDD system[20] were 0.45, 0.4, 0.4, 0.56, and 0.6 g/d, respectively.

In the JADER database, patient age is categorized in 10-year intervals; therefore, the defined daily dose (DDD) for the 0–9-year age group required adjustment relative to the adult DDD. We adjusted the DDD for this age group based on average body weight. Data on age-specific mean body weights were obtained from government statistics: for children aged 0–4 years, from the 2023 Infant and Young Children Growth Survey conducted by the Children and Families Agency,[22] and for those aged 5–9 years, from the 2024 School Health Statistics Survey conducted by the Ministry of Education, Culture, Sports, Science and Technology, Japan.[21, 23] Age-specific adjusted DDDs were calculated by multiplying the average body weight for each single-year age group by the maximum pediatric daily dose for each oral PCA (as specified in the respective package inserts in Japan; CFPN-PI: 9 mg/kg/day; CDTR-PI and CFTM-PI: 18 mg/kg/day; TBPM-PI: 12 mg/kg/day). Subsequently, DDDs were calculated in the same manner as for adults by dividing antimicrobial consumption by the adjusted DDD. The resulting values were then normalized by the population of the corresponding age group for fiscal year 2023 (8,927,000).[21]

The final adjusted DDDs for the 0–9-year age group were as follows: CFPN-PI, 0.17; CDTR-PI, 0.34; CFTM-PI, 0.34; and TBPM-PI, 0.15. To estimate antimicrobial use, total PCA consumption was expressed as defined daily doses per 1,000 inhabitants per day (DID). The annual DID was calculated as follows:

$$\text{DID (DDDs per 1,000 inhabitants per day)} = [\{\text{prescribed amounts (g)}\} / (\text{DDD} \times 365 \times \text{population})] \times 1{,}000$$

Table 1. Number and ROR of Hypocarnitinemia by PCAs and Other Drugs

Drug name	Case	Non-case	Total	ROR (95%CI)
β-lactams (PCAs)	252	4,024	4,276	1,300 (1,035-1,634)
Cefcapene pivoxil	101	2,521	2,622	345.2 (273.4-435.9)
Cefditoren pivoxil	113	1,190	1,303	858.7 (682.3-1,081)
Cefteram pivoxil	18	247	256	475.6 (291.3-776.4)
Tebipenem pivoxil	20	62	82	2,118 (1,265-3,545)
Pivmecillinam	0	4	4	-
β-lactams (non-PCAs)	0	8,856	8,856	-
Cephalosporins				
Cefaclor	0	611	611	-
Cefroxadine	0	8	8	-
Cephalexin	0	154	154	-
Cefatrizine	0	8	8	-
Cefadroxil	0	4	4	-
Cefuroxime axetil	0	126	126	-
Cefotiam	0	86	86	-
Cefpodoxime proxetil	0	283	283	-
Cefixime	0	61	61	-
Cefdinir	0	1,091	1,091	-
Ceftibuten	0	11	11	-
Penicillins				
Benzylpenicillin	0	9	9	-
Ampicillin	0	76	76	-
Amoxicillin	0	5,713	5,713	-
Bacampicillin	0	90	90	-
Sultamicillin tosilate	0	301	301	-
Carbapenems				
Faropenem	0	224	224	
Other drugs	107	2,212,771	2,212,878	0.0025 (0.0020-0.0031)
Adefovir pivoxil	0	1,623	1,623	-
Valproate	44	6,987	7,031	44.35 (32.33-60.89)
Carbamazepine	3	11,195	11,198	1.67 (0.53-5.19)
Cyproheptadine	3	234	237	80.14 (25.54-251.5)
Phenobarbital	3	2,185	2,188	8.58 (2.75-26.74)
Enteral nutritional supplements	3	49	52	382.8 (118.8-1,234)
Others	51	2,190,497	2,190,548	0.0027 (0.0020-0.0036)
Total	359	2,225,615	2,226,010	

ROR, reporting odds ratio; PCAs, pivalate-conjugated *β*-lactam antibiotics; 95%CI, 95% confidence interval

The total population data from 2014 to 2023 were obtained from the Statistics Bureau of Japan.[21] We calculated the median DID over a 10-year period and compared the values across different age groups. Statistical analyses were performed using the Kruskal-Wallis test followed by the Steel-Dwass test. $p < 0.05$ was considered statistically significant.

RESULTS

Signal Detection for Adverse Events Reports As shown in the primary dataset (Fig. 1), 898,584 patients and 6,568,343 cases of AEs were registered in JADER during the study period (Primary Dataset). In Dataset A, comprising a total of 2,226,010 cases, the number of hypocarnitinemia cases related to PCAs as the suspected drug was 252 cases.

Identification of Hypocarnitinemia Signals Associated with PCAs and Other Drugs The results of the univariate analysis on the safety signal for hypocarnitinemia are shown in Table 1. Among all antibiotics belonging to the *β*-lactam class, signals for hypocarnitinemia were detected only in the PCAs group, CFPN-PI, CDTR-PI, CFTM-PI, and TBPM-PI [ROR (95% CI); 345 (273-436), 859 (682-1,081), 476 (291-776), and 2,118 (1,265-3545), respectively]. In contrast, no cases were reported in other *β*-lactam antibiotics (non-PCAs). For drug groups other than antibiotics, a safety signal for hypocarnitinemia was detected only for VPA, enteral nutrition formula, and cyproheptadine. However, in cyproheptadine-related cases, two of the three drugs were co-administered with PCAs (CFPN-PI).

Univariate and Multivariate Analysis of Patients Who Developed Hypocarnitinemia Univariate and Multivariate logistic analyses were performed by extracting 352 cases who developed hypocarnitinemia in Dataset A (Table 2).

Among these patients, the onset of hypocarnitinemia was significantly associated with PCA users (ROR, 843; 95%CI [641, 1,107]; $p < 0.0001$), patients under 10 years of age (ROR, 21.2; 95%CI [16.5, 27.1]), and concomitant use of VPA (ROR, 34.4; 95%CI [25.1, 47.0]; $p < 0.0001$).

Assessment of Age-Specific PCA Utilization Using NDB Figure 2 shows the antibiotic usage index as DID per 1,000 inhabitants per day for antimicrobial consumption and the number of cases of hypocarnitinemia by age group. The

Table 2. Univariate and Multiple Logistic Regression Analysis for Hypocarnitinemia

Classification	Case (*n*)	Total (*n*)	RR[a] (%)	Univariate analysis		Multivariate analysis	
				ROR (95%CI)[b]	*p* value	ROR (95%CI)[b]	*p* value
PCA user	245	4,158	5.89	1,193 (948.7-1,501)	< 0.0001	843 (641-1,107)	< 0.0001
Non-PCA user	107	2,039,151	0.00523	1 [reference]	-	1 [reference]	-
Age < 10 years	248	90,312	0.275	51.71 (41.12-65.02)	<0.0001	21.2 (16.5-27.1)	< 0.0001
Age ≥ 10 years	104	1,952,997	0.00533	1 [reference]	-	1 [reference]	-
Female	189	1,002,664	0.0188	1.20 (0.98-1.48)	0.0832	1.18 (0.94-1.48)	0.146
Male	163	1,040,645	0.0157	1 [reference]	-	1 [reference]	-
Concomitant use of VPA-YES	81	45,028	0.180	13.29 (10.36-17.03)	< 0.0001	34.37 (25.14-46.98)	< 0.0001
Concomitant use of VPA-NO	271	1,998,281	0.0136	1 [reference]	-	1 [reference]	-

[a] RR = [Case/Total] × 100 (%), [b] 95% wald CI. RR, reporting ratio; ROR, reporting odds ratio; 95%CI, 95% confidence interval; PCA, pivalate-conjugated *β*-lactam antibiotic; VPA, valproate.

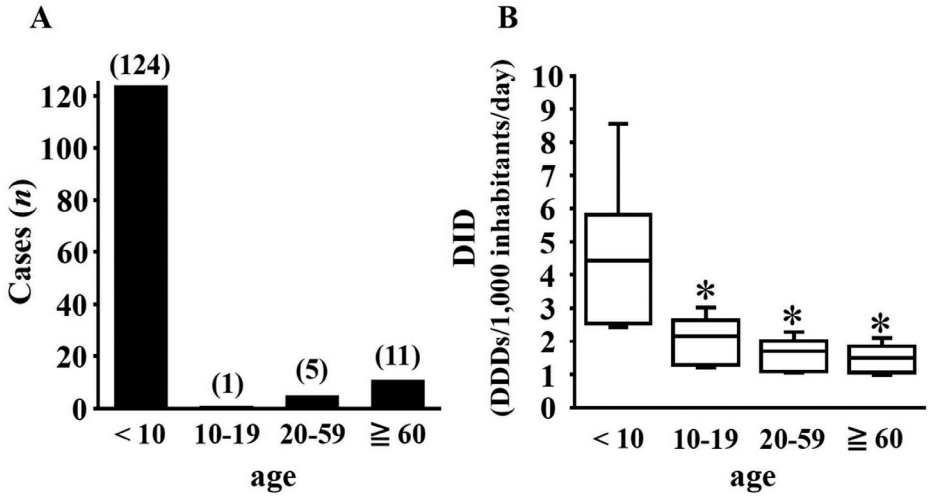

Fig. 2. Age-Group Distributions of (A) Number of Reported Cases of Hypocarnitinemia and (B) Median Antimicrobial Consumption of PCAs over the 10-Year Study Period, Expressed as Defined Daily Doses per 1,000 Inhabitants per Day (DID)

(A) The closed column represents cases of hypocarnitinemia in JADER by age group (fiscal year 2014-2023). (B) Box-and-whisker plots represent DID (DDDs per 1,000 inhabitants per day), which reflects the total annual PCA consumption. The DDD for each PCA was adjusted according to the age group of the patients (see Methods). The Kruskal-Wallis test was followed by the Steel-Dwass test for multiple comparisons. *$p < 0.05$ *vs*. "< 10".

number of hypocarnitinemia cases was the highest in patients under 10 years of age (Fig. 2A); the estimated antimicrobial consumption of PCAs in this age group was the highest across all age groups (Fig. 2B).

DISCUSSION

In this study, the onset of hypocarnitinemia was reported exclusively in patients receiving PCAs among *β*-lactam antibiotics, with most cases occurring in children under 10 years of age.

To our knowledge, this is the first nationwide disproportionality analysis evaluating PCA-associated hypocarnitinemia and comparing PCAs with other oral β-lactam antibiotics lacking a pivoxil moiety.

Most of the pivalic acid produced during the hydrolysis of PCAs in the body is combined with L-carnitine and excreted in the urine as pivaloylcarnitine. At this time, the concentration of free L-carnitine in the blood decreased for a short period. However, approximately 98% of carnitine in the body is distributed within the muscles, and carnitine deficiency symptoms are rare in adults with a large muscle mass. In contrast, children have low muscle mass, and when their energy needs are increased by fever due to infection, they may develop symptoms such as hypoglycemia, impaired consciousness, and convulsions due to impaired fatty acid *β*-oxidation, which is a serious symptom of hypocarnitinemia.[4)]

Brass *et al*. have reported in the study with healthy adults that plasma free carnitine levels declined to less than half of the baseline within a few days after the initiation of CFDN-PI.[3)] However, this decrease quickly recovered to normal levels when the administration of CFDN-PI was terminated. On the other hand, young children, including neonates, who have low carnitine stocks in the body to begin with, may be more prone to hypocarnitinemia than adults, as carnitine consumption and depletion in the body may be significant due to PCA administration and the development of infections resulting from this.

In the present study, a signal for hypocarnitinemia was detected in patients who received *β*-lactam antibiotics containing a pivoxil group. Reports of hypocarnitimemia were observed only for the PCAs within the *β*-lactams in the present dataset.

Based on the results of our analysis, we excluded multiple cases within a single patient, which resulted in the analysis of 48 cases in a dataset. Of these 48 cases, only 2 were more

than 10 years old, while the remaining were children under 10 years of age. In addition, more than 60% of cases developed hypocarnitinemia within one week of PCA administration. These findings suggest that careful monitoring for hypocarnitinemia may be warranted, particularly when PCAs are prescribed to children under 10 years of age. However, since serum carnitine concentrations are not routinely measured in clinical practice, hypocarnitinemia may be underdiagnosed and underreported, particularly among patients receiving antibiotics not generally recognized as causing carnitine depletion. Therefore, the absence of reported cases in non-PCA β-lactams should not be interpreted as evidence that hypocarnitinemia never occurs with these agents.

In a study using the Japan Medical Data Center (JMDC) database, which was established by a medical and pharmacy claims database, the onset of hypoglycemia, as a secondary cause of hypocarnitinemia, was associated with the use of PCAs.[13] These analyses were limited to children under the age of 5 years. In our present study, owing to the characteristics of the database used, the analysis was performed without age restrictions. The occurrence of hypocarnitinemia in older adult patients was observed in this study and previous case reports,[10] although to a lesser extent. Figure 2A showed that 11 cases of hypocarnitinemia were more than 60 years old, but the time-to-onset of hypocarnitinemia in older age groups could not be evaluated due to insufficient data on the duration of PCA use.

The multivariate analysis in Table 2 indicated that concomitant use of VPA was associated with the onset of hypocarnitinemia. Regarding the results in Table 2, when the study population was redefined as "under 10 years of age" and the data were reanalyzed using gender, use of PCA, and concomitant valproic acid as explanatory variables, significant associations were observed for all of these factors (see Supplementary Table). Based on these findings, further investigation is needed to determine whether gender differences are also observed in pediatric patients.

Possible mechanisms for the development of hypocarnitinemia with VPA administration include inhibition of renal reabsorption of L-carnitine by VPA, inhibition of L-carnitine synthase, and conversion of VPA to valproyl-CoA. This valproyl-CoA binds to carnitine similarly to PCAs and is excreted as valproylcarnitine.[24] Okumura *et al.* reported changes in serum free carnitine levels in six epilepsy patients (2-16 years) treated with VPA who received concomitant treatment with PCAs.[25] Three of those six patients had received carnitine supplementation before PCA and had free carnitine levels in the serum within the normal range. In the remaining three patients without carnitine supplementation, serum free carnitine levels fell below the normal range.

Especially for pediatric patients, concomitant use of VPA and PCA may result in a rapid decline in carnitine levels. Therefore, these findings suggest that patients receiving concomitant VPA may require careful clinical attention. Whether serum carnitine monitoring or prophylactic carnitine supplementation improves outcomes should be evaluated in future studies.

This study has some limitations. First, spontaneous reporting systems, such as the JADER database, are associated with various biases, including underreporting, overreporting, missing data, a lack of a denominator, and confounding factors. To address the lack of a denominator, we presented data that determined the number of PCAs prescribed and approximated the frequency of prescriptions (Fig. 2B). DID does not directly represent the number of exposed patients and therefore cannot be used to estimate the true incidence of hypocarnitinemia. The NDB analysis was performed solely to evaluate utilization patterns across age groups. These data suggested that the difference in the number of cases by age group may not be due to differences in the PCA prescription frequency.

Second, since fiscal year 2012, warnings regarding the onset of hypocarnitinemia associated with PCA use in children have been issued by the PMDA and the Japan Pediatric Society.[9,26] Therefore, the rise in reported hypocarnitinemia cases after the 2012 fiscal year suggests the possibility of notoriety bias,[27] whereby increased awareness following safety alerts may have stimulated reporting of hypocarnitinemia.

Conclusion Our findings suggest that the use of β-lactam antibiotics containing a pivoxil moiety is disproportionately associated with reports of hypocarnitinemia in the JADER database. These findings should be interpreted as hypothesis-generating, and further epidemiological studies are warranted to confirm these associations. Careful monitoring for hypocarnitinemia may be appropriate, particularly in children under 10 years of age and patients co-administered VPA.

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Conflict of interest The authors declare no conflict of interest.

Authors' contributions All authors meet the ICMJE authorship criteria. ST, RS, and TY conceived and designed the study. ST, RS, MT, and NH were responsible for the data acquisition, analysis, and interpretation. ST and RS prepared the initial draft of the manuscript, and NI and TY revised it. All the authors have read and approved the final manuscript.

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