Annals of Clinical Epidemiology

SHORT REPORT

Prescription and Therapeutic Drug Monitoring Status of Valproic Acid among Patients Receiving Carbapenem Antibiotics: A Preliminary Survey Using a Japanese Claims Database

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KEY WORDS

drug-drug interactions, valproic acid, carbapenem antibiotics, insurance claims, therapeutic drug monitoring

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Received: March 2, 2021 Accepted: May 30, 2021
No. 22002

INTRODUCTION

Drug-drug interaction with carbapenem antibiotics (CBAs) is an important issue in valproic acid (VPA) administration because CBAs can reduce the serum concentration of VPA by over 50% [1, 2]. A recent review suggested that co-administration of CBAs and VPA should be avoided [3]. Indeed, the package insert and label of VPA in the U.S.A. and Japan describe this combination as "contraindications for co-administration" and "PRECAUTIONS", respectively [4, 5]. As CBAs have a broad-spectrum antibacterial effect, they are important infection therapy drugs [6]. Therefore, therapeutic drug monitoring (TDM) of VPA concentrations should be implemented if co-administration of VPA and CBAs is clinically required [3].

However, the prescription status of the concomitant use of CBA and VPA is unknown, and appropriate TDM implementation has not been investigated. Recently, large health insurance claims databases have been employed for research purposes. Although claims databases cannot show actual drug use, they can be used to assess prescription status.

Therefore, as a preliminary study, we conducted a cross-sectional survey of the prescription status of concomitant CBA and VPA use and of TDM implementation status using a Japanese claims database.

METHODS

Data Sources

We employed the JMDC claims database constructed by

JMDC, Inc. (Tokyo, Japan) [7]. This database contains Japanese health insurance claims at medical institutions and pharmacies from employees of medium-sized or large companies and their family members under 75 years of age. The database comprises data for approximately 7.3 million individuals registered in 2020, but does not contain laboratory data.

Study Population and Outcomes

Patients who received intravenous injections of CBA during hospitalization for more than 2 days between April 2010 and March 2017 were included. Meropenem, doripenem, imipenem/cilastatin, biapenem, and panipenem/betamipron were evaluated; these are injectable CBAs that can be prescribed in Japan.

As the primary endpoint, the proportion of prescriptions for concomitant VPA and CBA use was evaluated. In addition, in patients who concomitantly received CBA and VPA, the following outcomes were evaluated: (1) TDM implementation for VPA from the start to the end of CBA therapy; and (2) daily VPA dose changes at the start and end of CBA therapy in patients who did not discontinue VPA during CBA administration. Patients for whom VPA administration was discontinued were also included in the calculation of the TDM proportion, as TDM should be implemented in these patients [3].

Concomitant drugs were detected from overlapping prescription periods. If a single patient received multiple rounds of CBA therapy during the study period (e.g., receiving CBAs in April 2010 and October 2015), only the first administration was included. As the JMDC claims database does not contain laboratory data (i.e., serum VPA concentrations), TDM implementation was detected by identifying the related medical fee, named "specific drug treatment management fee" [8]. However, this medical fee can be attributable to target drugs other than VPA [8]; that is, even if this fee is calculated during CBA therapy, it may be aimed at a drug other than VPA. Therefore, we also evaluated the status of concomitant drugs targeted with a "specific drug treatment management fee" for each patient. Consequently, TDM implementation for VPA was assessed only for patients who did not receive other drugs that incur a "specific drug treatment management fee." As CBA reduces the serum concentration of VPA within 24 h [1, 2], we assessed TDM implementation from the start of CBA therapy.

Data Collection

Anatomical Therapeutic Chemical system codes were used to identify drugs: J01DH02 (meropenem), J01DH04 (doripenem), J01DH51 (imipenem/cilastatin), J01DH05 (biapenem), J01DH55 (panipenem/betamipron), and N03AG01 (VPA). In addition, daily VPA dosage was measured. Moreover, concomitant drugs with a "specific drug treatment management fee" were detected [8]; their details are shown in **Supplementary Table 1**.

The primary diseases for which VPA was prescribed were identified from the diagnostic fields using the International Classification of Diseases, Tenth Revision (ICD-10) codes and were as follows: epilepsy (ICD-10 code: G40), bipolar disorder (ICD-10 code: F309, F319), and migraine (ICD-10 code: G43). Demographic data, such as patient age, sex (male/female), CBA therapy duration, performance status of blood culture test on the day of CBA administration or the day before, and medical fees related to TDM (i.e., "specific drug treatment management fees") were collected.

Data Analyses

Continuous variables were expressed as the mean ± standard deviation. The daily doses of VPA at the start and end of CBA therapy were compared using a two-tailed paired *t*-test. A *P*-value <0.05 indicated a significant difference. JMP 14® software (SAS Institute, Inc., Cary, NC, USA) was used for all data analyses.

Ethics

This study was reviewed by the Institutional Review Board of the Faculty of Pharmaceutical Sciences of Hokkaido University. As all data were anonymized, the requirement for informed consent was waived for our study (an approval number was not provided).

RESULTS

Prescription Status of Concomitant CBA and VPA

Among patients who received intravenous injections of CBA for more than 2 days between April 2010 and March 2017 (inclusive; n = 14,118), 173 patients (1.23%) were prescribed VPA (**Fig. 1**).

Among patients who concomitantly received CBAs and VPA (**Table 1**, n = 173), meropenem was the most commonly prescribed CBA (n = 117, 67.6%). The primary disease for which VPA was most frequently prescribed was epilepsy (n = 139, 80.3%). The proportion of concomitant drugs that incurred a "specific drug treatment management fee" was 65.3% (**Supplementary Table 2**). Blood culture tests were performed in 45 patients (26.0%).

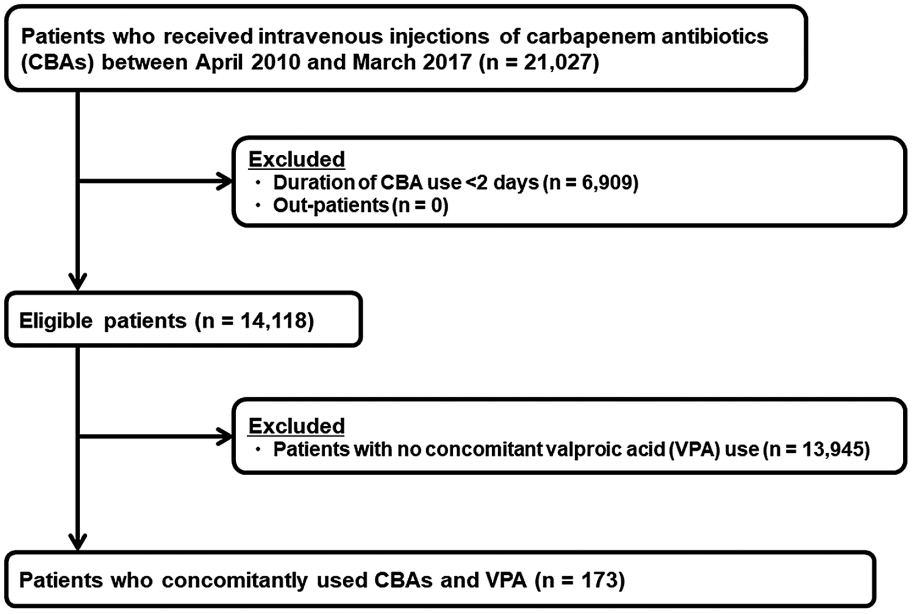


Fig. 1 Flowchart of patients included in this study and status of valproic acid prescription for patients who also received carbapenem antibiotics

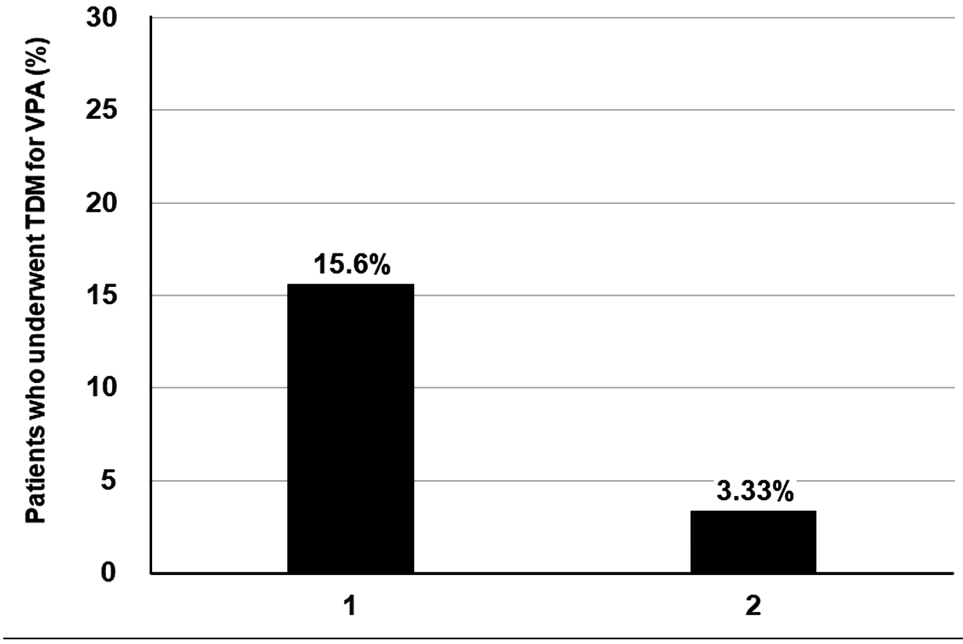
Table 1 Characteristics of patients who concomitantly received CBAs and VPA (n = 173).

Description	Value
Age (years), mean ± SD	42.4 ± 20.7
Sex (male), n (%)	103 (59.5)
CBAs, n (%)	
Meropenem	117 (67.6)
Doripenem	23 (13.3)
Imipenem/cilastatin	16 (9.25)
Biapenem	1 (0.58)
Panipenem/betamipron	16 (9.25)
Duration of CBA therapy (days), mean ± SD	7.81 ± 6.97
Performance of blood culture tests on the day of CBA administration or the day before, n (%)	45 (26.0)
Concomitant drug use with "specific drug treatment management fee," n (%)	113 (65.3)
Primary diseases for which VPA was prescribed, n (%)†	
Epilepsy	139 (80.3)
Bipolar disorder	28 (16.2)
Migraine	13 (7.51)

† Overlap in primary diseases. CBAs: carbapenem antibiotics, VPA: valproic acid, SD: standard deviation.

TDM Implementation Status

In patients receiving CBA and VPA, TDM implementation was conducted in 15.6% of patients (27 of 173) (**Fig. 2**). Among patients who did not receive other concomitant drugs incurring a "specific drug treatment management fee," 3.33% (2 of 60) underwent TDM.



Patterns	Evaluated patients (n)
1	Patients who concomitantly received CBAs and VPA (n = 173)
2	In pattern 1, patients who did not use any other concomitant medications with a "specific drug treatment management fee" (n = 60)

Fig. 2 **Proportion of TDM implementation for VPA during CBA therapy**

TDM: therapeutic drug monitoring, VPA: valproic acid, CBAs: carbapenem antibiotics.

Changes in the Daily Dose of VPA

Among patients receiving CBA and VPA (n = 173), 23 discontinued VPA during CBA administration. In patients who continued VPA (n = 150), the daily dose was increased in 6 patients and decreased in 1 patient. The daily dose of VPA at the start and end of CBA therapy showed no significant difference (635.2 ± 353.7 mg vs 645.0 ± 360.8 mg, respectively; P = 0.370, two-tailed paired t-test).

DISCUSSION

Seizures occur in 48.1–54.5% of patients who received CBA and VPA [1, 9]. Thus, the clinical importance of this drug-drug interaction has been established, although we could not evaluate the occurrence of seizure events. We also evaluated patients with bipolar disorder and migraine because the serum concentrations of VPA and the clinical effects of these diseases are associated [10, 11].

We observed that 1.23% of patients who received CBA were prescribed VPA. As there were no comparable data, it was difficult to assess whether this proportion is high or low. However, considering the guideline recommendation [3], it is important to evaluate whether the risk posed by this combination has been recognized by clinicians and pharmacists. The proportion of TDM implementation for VPA assessed by identifying the "specific drug treatment management fee" was 15.6%. As described above, this medical fee may have been used for other targeted drugs [8]; thus, there is a high possibility of overestimation. Therefore, we also evaluated patients not on other concomitant drugs incurring this medical fee; the proportion was only 3.33%. Indeed, vancomycin, an anti-methicillin-resistant *Staphylococcus aureus* agent, is a major, commonly used concomitant drug (**Supplementary Table 2**) [12]. Accordingly, we found that clinicians and pharmacists do not appropriately manage this important drug-drug interaction. In fact, the daily dose

of VPA was unchanged in most cases. For recognizing and avoiding important drug–drug interactions, computerized alert systems may be useful [13]. However, as these systems create the burden of numerous reminders and alerts, clinicians often override not only non-important alerts, but also important alerts [14], which may be related to the low proportion of TDM implementation observed in our study. In addition, inappropriate use of CBAs may be associated with a low proportion of TDM implementation [15]. Indeed, the proportion of blood culture tests performed on the day of administration of CBAs or the day before was only 26.0%.

Our study has several limitations. First, actual drug use and accuracy of diagnosis could not be evaluated. Second, as the JMDC claims database contains data for patients aged <75 years only, older patients were not evaluated. Third, as the database does not contain laboratory data, some important information could not be evaluated. Fourth, it is possible that some facilities routinely calculate a "specific drug treatment management fee" once a month for patients who use relevant medications. Fifth, as the JMDC claims database comprises data on employees and their families, our study has a risk of selection bias caused by the medical systems and human resources (i.e., computerized alert systems and hospital pharmacists) of the hospitals. Finally, we could not evaluate the most recent status because the database contained data only up to June 2017.

CONCLUSIONS

This preliminary survey suggests that clinicians and pharmacists do not appropriately manage drug-drug interactions between CBA and VPA. Additional studies, including data on "actual drug use" and "elderly patients," are required.

CONFLICTS OF INTEREST

The authors declare no conflict of interests.

ACKNOWLEDGMENTS

None.

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